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=> fil reg
FILE 'REGISTRY' ENTERED AT 14:47:57 ON 17 MAR 2006
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=> d his

     (FILE 'HOME' ENTERED AT 11:00:13 ON 17 MAR 2006)

     FILE 'HCAPLUS' ENTERED AT 11:00:18 ON 17 MAR 2006
                E US20040023981/PN
L1            1 S E3
                SEL RN

     FILE 'REGISTRY' ENTERED AT 11:02:31 ON 17 MAR 2006
L2           59 S E1-59

     FILE 'HCAPLUS' ENTERED AT 11:22:21 ON 17 MAR 2006
                E REN YU/AU
L3           67 S E3
                E KARKI ?/AU
                E KARKI S?/AU
L4           14 S E12
L5            1 S E13
                E ZHAO M?/AU
L6           16 S E48
                E BILODEAU M?/AU
L7           62 S E8
L8            1 S E9
L9            1 S L3 AND L4 AND L6 AND L7
L10       42761 S TYROSINE#(3A)KINASE#
L11           2 S L3 AND L10
L12           5 S L4 AND L10
L13           5 S L6 AND L10
L14          22 S L7 AND L10
L15           4 S L14 AND SALT#
L16          11 S L11 OR L12 OR L13 OR L15
L17          17 S L14 NOT L16

     FILE 'REGISTRY' ENTERED AT 11:49:48 ON 17 MAR 2006
                E C16H19N7OS
L18          38 S E3
L19          25 S L18 AND 3/NR
L20        7543 S 64-17-5/CRN
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L21          10 S 479611-82-0/CRN
L22           5 S L21 AND 2/NC
L23           1 S L21 AND L20
L24           3 S L21 AND (H(L)CL)/ELS
L25           6 S L22 OR L23
L26           7 S L25 OR L24

     FILE 'HCAPLUS' ENTERED AT 14:16:26 ON 17 MAR 2006
L27           2 S L26
L28           2 S L21
L29           2 S L27 OR L28

     FILE 'REGISTRY' ENTERED AT 14:47:57 ON 17 MAR 2006

=> fil hcap
FILE 'HCAPLUS' ENTERED AT 14:48:07 ON 17 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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=> d l16 ibib abs hitstr hitind 1-11

L16  ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:857555  HCAPLUS
DOCUMENT NUMBER:          141:337784
TITLE:                    Formulations for tyrosine
                          kinase inhibitors
INVENTOR(S):              Karki, Shyam B.; Deshpande, Sameer R.;
                          Thompson, Karen C.; Payne, Anne H.; Gandek,
                          Thomas P.
PATENT ASSIGNEE(S):       Merck & Co. Inc., USA
SOURCE:                   PCT Int. Appl., 21 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
     ---------------      ----   --------    --------------------
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     WO 2004087651         A2    20041014    WO 2004-US8828
                                                                   200403
                                                                   23
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WO 2004087651 A3 20041216
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2519106 AA 20041014 CA 2004-2519106 200403 23

EP 1610614 A2 20060104 EP 2004-758216 200403 23
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK

PRIORITY APPLN. INFO.: US 2003-458094P P 200303 27

WO 2004-US8828 W 200403 23

AB The present invention is related to a powder, powder blend or granulation formulation of 3-[5-(4-methanesulfonylpiperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one (I), a **tyrosine kinase** inhibitor, which is adapted for reconstitution with a diluent. This invention is also related to an aq. suspension, or a dispersion, particularly to a stable oral pharmaceutical formulation, comprising granules of I mixed with a diluent. Thus, a formulation contained I 1080.0, Avicel PH101 800.0, lactose 1860.0, Klucel EXF 120.0, AcDiSol 120.0, and Mg stearate 20.0 mg/bottle.

IC ICM C07D
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 27
ST **tyrosine kinase** inhibitor indolylquinolinone prepn; quinolinone indole **tyrosine kinase** inhibitor prepn

IT Antitumor agents
Binders
Buffers
Fillers
Flavor
Human
Lubricants
Neoplasm
Stabilizing agents
Sweetening agents
Syrups (sweetening agents)
(formulations for **tyrosine kinase** inhibitors)

IT Drug delivery systems
(granules; formulations for **tyrosine kinase** inhibitors)

IT Viscosity
(modifiers; formulations for **tyrosine kinase** inhibitors)

IT Drug delivery systems
(oral; formulations for **tyrosine kinase** inhibitors)

IT Drug delivery systems
(powders; formulations for **tyrosine kinase** inhibitors)

IT Drug delivery systems
(tablets; formulations for **tyrosine kinase** inhibitors)

IT 939-16-2 5419-55-6 15861-24-2, 1H-Indole-5-carbonitrile 24424-99-5 57260-71-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(formulations for **tyrosine kinase** inhibitors)

IT 279256-09-6P 479065-28-6P 771477-41-9P 771477-42-0P 771477-43-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(formulations for **tyrosine kinase** inhibitors)

IT 335649-90-6P 415684-58-1P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(formulations for **tyrosine kinase** inhibitors)

IT 63-42-3, Lactose 69-65-8, Mannitol 9004-64-2, Hydroxypropyl cellulose 74811-65-7, Croscarmellose sodium 149691-08-7, Dipac 345660-09-5, Ora Plus 345660-10-8, Ora Sweet
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulations for **tyrosine kinase** inhibitors)

IT 80449-02-1
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; formulations for **tyrosine kinase** inhibitors)
IT 9004-34-6, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (microcryst.; formulations for **tyrosine kinase** inhibitors)

L16 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:100813 HCAPLUS
DOCUMENT NUMBER: 140:151963
TITLE: Salt forms with **tyrosine kinase** activity
INVENTOR(S): **Ren, Yu; Karki, Shyam B.; Zhao, Matthew M.**; Bidodeau, Mark T.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 37 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004023981	A1	20040205	US 2003-607114	20030626
PRIORITY APPLN. INFO.:			US 2002-398263P	P 20020724

AB The present invention relates to salt forms of 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide (I) which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction, and compns. which contain these compds. Methods of using them to treat **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age-related macular degeneration, diabetic retinopathy, retinal ischemia, macular edema, and inflammatory diseases in mammals. Thus, I was prepd. by the reaction of a piperazine urea with formylpryridine-contg. aminothiazole deriv. followed by redn. The

crystal structures of salts of I were studied.
IC ICM A61K031-496
ICS C07D417-14
INCL 514253100; 544360000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 28
ST **tyrosine kinase** salt piperazinecarboxylic acid methylamide prepn
IT Troponins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Troponin-1; salt forms with **tyrosine kinase** activity)
IT Lung, neoplasm
(adenocarcinoma; salt forms with **tyrosine kinase** activity)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; salt forms with **tyrosine kinase** activity)
IT Lymphatic system, disease
Urogenital system, disease
(cancer; salt forms with **tyrosine kinase** activity)
IT Mammary gland, neoplasm
(carcinoma; salt forms with **tyrosine kinase** activity)
IT Dermatitis
(contact; salt forms with **tyrosine kinase** activity)
IT Allergy
(delayed hypersensitivity; salt forms with **tyrosine kinase** activity)
IT Eye, disease
(diabetic retinopathy; salt forms with **tyrosine kinase** activity)
IT Neuroglia, neoplasm
(glioblastoma; salt forms with **tyrosine kinase** activity)
IT Lymphoma
(histiocytic; salt forms with **tyrosine kinase** activity)
IT Platelet-derived growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; salt forms with **tyrosine kinase** activity)

IT Eye, disease
(macula, edema; salt forms with **tyrosine kinase** activity)
IT Eye, disease
(macula, senile degeneration; salt forms with **tyrosine kinase** activity)
IT Carcinoma
(mammary; salt forms with **tyrosine kinase** activity)
IT Androgen receptors
Estrogen receptors
Retinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulators; salt forms with **tyrosine kinase** activity)
IT Bone, neoplasm
Sarcoma
(osteosarcoma; salt forms with **tyrosine kinase** activity)
IT Carcinoma
(pulmonary adenocarcinoma; salt forms with **tyrosine kinase** activity)
IT Carcinoma
(pulmonary small-cell; salt forms with **tyrosine kinase** activity)
IT Eye
(retina, vascularization; salt forms with **tyrosine kinase** activity)
IT Eye, disease
(retinal ischemia; salt forms with **tyrosine kinase** activity)
IT Ischemia
(retinal; salt forms with **tyrosine kinase** activity)
IT Angiogenesis inhibitors
Antitumor agents
Brain, neoplasm
Eye, disease
Hygroscopicity
Inflammation
Larynx, neoplasm
Lung, neoplasm
Neoplasm
Osteoarthritis
Pancreas, neoplasm

Polymorphism (crystal)
Powder x-ray diffractometry
Psoriasis
Radiotherapy
Rheumatoid arthritis
Rickets
Signal transduction, biological
Stomach, neoplasm
(salt forms with **tyrosine kinase** activity)

IT Interleukin 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salt forms with **tyrosine kinase** activity)

IT Lung, neoplasm
(small-cell carcinoma; salt forms with **tyrosine kinase** activity)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; salt forms with **tyrosine kinase** activity)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αIIbβ3, antagonists; salt forms with **tyrosine kinase** activity)

IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, agonist; salt forms with **tyrosine kinase** activity)

IT 39391-18-9, Cyclooxygenase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; salt forms with **tyrosine kinase** activity)

IT 9028-35-7, HMG-CoA reductase 9068-38-6, Reverse transcriptase 62229-50-9, Epidermal growth factor 80449-02-1, **Tyrosine kinase** 127464-60-2, Vascular endothelial growth factor 131384-38-8, Prenylprotein transferase 141907-41-7, Matrix metalloproteinase 144114-21-6, HIV protease 329900-75-6, COX-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; salt forms with **tyrosine kinase** activity)

IT 479611-82-0P 652156-19-9P 652156-20-2P 652156-21-3P 652156-22-4P 652156-23-5P 652156-24-6P 652156-25-7P 652156-26-8P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(salt forms with **tyrosine kinase** activity)

IT 62-56-6, Thiourea, reactions 74-89-5, Methylamine, reactions 624-83-9, Methyl isocyanate 1079-66-9 1885-14-9, Phenyl chloroformate 5327-32-2 19814-75-6 57260-71-6 69194-03-2 69194-04-3 101066-61-9 163361-25-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(salt forms with **tyrosine kinase** activity)

IT 2759-28-6P 6937-03-7P 51640-36-9P 51640-52-9P 54221-95-3P 85989-62-4P 105250-17-7P 161265-03-8P, Xantphos 329794-09-4P 329794-13-0P 329794-14-1P 329794-15-2P 479611-85-3P 652154-14-8P 652154-15-9P 652154-16-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(salt forms with **tyrosine kinase** activity)

IT 50-35-1, Thalidomide 10540-29-1, Tamoxifen 33069-62-4, Paclitaxel 37300-21-3, Pentosan polysulfate 84449-90-1, Raloxifene 86090-08-6, Angiostatin 99519-84-3 117048-59-6, Combretastatin A-4 144494-65-5, Tirofiban 148717-90-2, Squalamine 180288-69-1, Trastuzumab 561321-04-8, 6-O-Chloroacetyl-carbonyl)-fumagillol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salt forms with **tyrosine kinase** activity)

L16 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:100812 HCAPLUS
DOCUMENT NUMBER: 140:151962
TITLE: Polymorphs with **tyrosine kinase** activity
INVENTOR(S): **Zhao, Matthew M.**; Bilodeau, Mark T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004023980	A1	20040205	US 2003-607091	20030626
US 6872724	B2	20050329		
PRIORITY APPLN. INFO.:			US 2002-398238P	P 20020207

AB The present invention relates to active polymorphs of 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide (I) which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction, and compns. which contain these compds. Methods of using them to treat **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age-related macular degeneration, diabetic retinopathy, retinal ischemia, macular edema, and inflammatory diseases in mammal are also disclosed. Thus, I was prepd. by the reaction of BOC-piperazine with Me isocyanate followed by deprotection and reaction with 2-(4-chloromethylpyridin-2-ylamino)th-5-carbonitrile. The crystal structure of a I polymorph was studied.

IC ICM A61K031-496
ICS C07D417-14

INCL 514253100; 544360000

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 28

ST **tyrosine kinase** polymorph piperazinecarboxylic acid methylamide prepn

IT Lung, neoplasm
(adenocarcinoma; polymorphs with **tyrosine kinase** activity)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; polymorphs with **tyrosine kinase** activity)

IT Lymphatic system, disease
Urogenital system, disease
(cancer; polymorphs with **tyrosine kinase** activity)

IT Mammary gland, neoplasm
(carcinoma; polymorphs with **tyrosine kinase** activity)

IT Ischemia
(cerebral; polymorphs with **tyrosine kinase** activity)

IT Dermatitis
(contact; polymorphs with **tyrosine kinase** activity)

IT Allergy
(delayed hypersensitivity; polymorphs with **tyrosine kinase** activity)

IT Eye, disease
(diabetic retinopathy; polymorphs with **tyrosine kinase** activity)
IT Neuroglia, neoplasm
(glioblastoma; polymorphs with **tyrosine kinase** activity)
IT Lymphoma
(histiocytic; polymorphs with **tyrosine kinase** activity)
IT Platelet-derived growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; polymorphs with **tyrosine kinase** activity)
IT Brain, disease
(ischemia; polymorphs with **tyrosine kinase** activity)
IT Eye, disease
(macula, edema; polymorphs with **tyrosine kinase** activity)
IT Eye, disease
(macula, senile degeneration; polymorphs with **tyrosine kinase** activity)
IT Carcinoma
(mammary; polymorphs with **tyrosine kinase** activity)
IT Androgen receptors
Estrogen receptors
Retinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulator; polymorphs with **tyrosine kinase** activity)
IT Bone, neoplasm
Sarcoma
(osteosarcoma; polymorphs with **tyrosine kinase** activity)
IT Angiogenesis
Angiogenesis inhibitors
Antitumor agents
Brain, neoplasm
Eye, disease
Inflammation
Larynx, neoplasm
Lung, neoplasm
Neoplasm
Osteoarthritis

Pancreas, neoplasm
Polymorphism (crystal)
Powder x-ray diffractometry
Psoriasis
Radiotherapy
Rheumatoid arthritis
Rickets
Signal transduction, biological
Stomach, neoplasm
(polymorphs with **tyrosine kinase** activity)

IT Interleukin 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polymorphs with **tyrosine kinase** activity)

IT Carcinoma
(pulmonary adenocarcinoma; polymorphs with **tyrosine kinase** activity)

IT Carcinoma
(pulmonary small-cell; polymorphs with **tyrosine kinase** activity)

IT Eye, disease
(retinal ischemia; polymorphs with **tyrosine kinase** activity)

IT Ischemia
(retinal; polymorphs with **tyrosine kinase** activity)

IT Lung, neoplasm
(small-cell carcinoma; polymorphs with **tyrosine kinase** activity)

IT Troponins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(troponin 1; polymorphs with **tyrosine kinase** activity)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; polymorphs with **tyrosine kinase** activity)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αIIbβ3, antagonists; polymorphs with **tyrosine kinase** activity)

IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, agonists; polymorphs with **tyrosine kinase** activity)

IT 127464-60-2, Vascular endothelial growth factor

RL: BSU (Biological study, unclassified); BIOL (Biological study) (antibodies to; polymorphs with **tyrosine kinase** activity)

IT 9028-35-7, HMG-CoA reductase 9068-38-6, Reverse transcriptase 62229-50-9, Epidermal growth factor 131384-38-8, Prenylprotein transferase 144114-21-6, HIV protease
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor; polymorphs with **tyrosine kinase** activity)

IT 39391-18-9, Cyclooxygenase 141907-41-7, Matrix metalloproteinase 329900-75-6, COX-2
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; polymorphs with **tyrosine kinase** activity)

IT 80449-02-1, **Tyrosine kinase** 99519-84-3
RL: BSU (Biological study, unclassified); BIOL (Biological study) (polymorphs with **tyrosine kinase** activity)

IT 479611-82-0P, 4-[2-(5-Cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-car boxylic acid methylamide
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (polymorphs with **tyrosine kinase** activity)

IT 62-56-6, Thiourea, reactions 74-89-5, Methylamine, reactions 624-83-9 1079-66-9 1885-14-9, Phenyl chloroformate 2759-28-6 5327-32-2 19814-75-6 57260-71-6 69194-03-2 69194-04-3 101066-61-9
RL: RCT (Reactant); RACT (Reactant or reagent) (polymorphs with **tyrosine kinase** activity)

IT 6937-03-7P 51640-36-9P 51640-52-9P 54221-95-3P 85989-62-4P 105250-17-7P 161265-03-8P 163361-25-9P 329794-09-4P 329794-13-0P 329794-14-1P 329794-15-2P 479611-85-3P 652154-14-8P 652154-15-9P 652154-16-0P 652156-53-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (polymorphs with **tyrosine kinase** activity)

IT 50-35-1, Thalidomide 10540-29-1, Tamoxifen 33069-62-4, Paclitaxel 37300-21-3, Pentosan polysulfate 84449-90-1, Raloxifene 86090-08-6, Angiostatin 117048-59-6, Combretastatin A-4 144494-65-5, Tirofiban 148717-90-2, Squalamine 180288-69-1, Trastuzumab 561321-04-8, 6-O-Chloroacetylcarbonyl)fumagillol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (polymorphs with **tyrosine kinase** activity)

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE

IN THE RE FORMAT

L16 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:100811 HCAPLUS
DOCUMENT NUMBER: 140:146127
TITLE: Process for making substituted thiazolyl-amino pyridines
INVENTOR(S): **Zhao, Matthew M.**; Yin, Jingjun
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004023979	A1	20040205	US 2003-607056	20030626
PRIORITY APPLN. INFO.:			US 2002-395837P	P 20020715

OTHER SOURCE(S): CASREACT 140:146127; MARPAT 140:146127
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to a process for prepg. substituted thiazolyl-amino pyridines (I) [R = H, each (un)substituted C1-10 alkyl or aryl; R1 = CONHR3; R2 = H, OH, C1-6 alkoxy, C1-6 alkyl, halo; R3 = C1-6 alkyl] which are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type **tyrosine kinases** and may be used to treat **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, or inflammatory diseases in mammals. The above process comprises (a) prepg. a slurry of 2-aminothiazole-5-carbonitrile (II)

(where R is defined above), 2-halopyridine-4-carbaldehyde (III) (where X = a halo; R2 is defined above) and a base in a solvent, (b) adding a palladium catalyst and a bisphosphine ligand to the slurry to produce a coupling product of 2-[(4-formyl-2-pyridyl)amino]thiazole-5-nitrile (IV), (c) adding a piperazine-urea of formula (V) (R3 is defined above) to the coupling product of formula IV; and (d) completing a reductive amination to produce the compd. of formula I. Thus, in a 2-3 kg scale reaction, 2-chloro-4-formylpyridine was coupled with 2-aminothiazole in the presence of Pd(dba)3, 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, and K3PO4 in toluene-water at 90° for 8 h to give 97% 2-[(4-formyl-2-pyridyl)amino]thiazole-5-nitrile which underwent reductive coupling with N-(methylaminocarbonyl)piperazine hydrochloride using NaBH(OAc)2 in the presence of Et3N and AcOH in N,N-dimethylacetamide for a total of 260 min to give 80.4% the title compd. (VI). The compds. I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01-5.0 μM.

IC ICM A61K031-496
ICS C07D417-14
INCL 514253100; 544360000
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7
ST thiazolylaminopyridine prepn **tyrosine kinase** inhibitor modulator regulator
IT Antiarteriosclerotics
(antiatherosclerotics; prepn. of thiazolylaminopyridines as inhibitors, modulators and/or regulators **tyrosine kinases** for treatment of **tyrosine kinase**-dependent diseases)
IT Eye, disease
(diabetic retinopathy; prepn. of thiazolylaminopyridines as inhibitors, modulators and/or regulators **tyrosine kinases** for treatment of **tyrosine kinase**-dependent diseases)
IT Eye, disease
(macula, senile degeneration; prepn. of thiazolylaminopyridines as inhibitors, modulators and/or regulators **tyrosine kinases** for treatment of **tyrosine kinase**-dependent diseases)
IT Angiogenesis
Angiogenesis inhibitors
Anti-inflammatory agents
Antitumor agents
Atherosclerosis

Human
Inflammation
Neoplasm
(prepn. of thiazolylaminopyridines as inhibitors, modulators and/or regulators **tyrosine kinases** for treatment of **tyrosine kinase**-dependent diseases)

IT 386705-49-3, VEGF receptor **tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of thiazolylaminopyridines as inhibitors, modulators and/or regulators **tyrosine kinases** for treatment of **tyrosine kinase**-dependent diseases)

L16 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:100810 HCAPLUS
DOCUMENT NUMBER: 140:151961
TITLE: Active **salt** forms with **tyrosine kinase** activity
INVENTOR(S): **Ren, Yu; Karki, Shyam B.; Zhao, Matthew M.; Bilodeau, Mark T.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004023978	A1	20040205	US 2003-607031	20030626
PRIORITY APPLN. INFO.:			US 2002-398236P	P 20020724

AB The present invention relates to orally active **salt** forms of the mesylate **salt** of 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide (I) which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction and compns. which contain these

compds. Methods of using them to treat **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, retinal ischemia, macular edema, and inflammatory diseases in mammals are also disclosed. Thus, I was prepd. by the reaction of a piperazine urea with formylpyridine-contg. aminothiazole deriv. followed by redn. The crystal structures of **salts** of I were studied.

IC ICM A61K031-496
ICS C07D417-14
INCL 514253100; 544360000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 28
ST **tyrosine kinase salt**
piperazinecarboxylic acid methylamide prepn
IT Angiogenesis
Angiogenesis inhibitors
Antitumor agents
Brain, neoplasm
Eye, disease
Hygroscopicity
Inflammation
Larynx, neoplasm
Lung, neoplasm
Neoplasm
Osteoarthritis
Osteoarthritis
Pancreas, neoplasm
Polymorphism (crystal)
Powder x-ray diffractometry
Psoriasis
Radiotherapy
Rheumatoid arthritis
Rickets
Rickets
Solubility
Stomach, neoplasm
(active **salt** forms with **tyrosine kinase** activity)
IT Interleukin 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(active **salt** forms with **tyrosine kinase** activity)
IT Lung, neoplasm
(adenocarcinoma; active **salt** forms with

tyrosine kinase activity)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blockers; active **salt** forms with **tyrosine kinase** activity)
IT Lymphatic system, disease
Urogenital system, disease
(cancer; active **salt** forms with **tyrosine kinase** activity)
IT Mammary gland, neoplasm
(carcinoma; active **salt** forms with **tyrosine kinase** activity)
IT Ischemia
(cerebral; active **salt** forms with **tyrosine kinase** activity)
IT Dermatitis
(contact; active **salt** forms with **tyrosine kinase** activity)
IT Allergy
(delayed hypersensitivity; active **salt** forms with **tyrosine kinase** activity)
IT Eye, disease
(diabetic retinopathy; active **salt** forms with **tyrosine kinase** activity)
IT Growth factors, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fibroblast-derived growth factors, inhibitor; active **salt** forms with **tyrosine kinase** activity)
IT Neuroglia, neoplasm
(glioblastoma; active **salt** forms with **tyrosine kinase** activity)
IT Lymphoma
(histiocytic; active **salt** forms with **tyrosine kinase** activity)
IT Platelet-derived growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; active **salt** forms with **tyrosine kinase** activity)
IT Brain, disease
(ischemia; active **salt** forms with **tyrosine kinase** activity)
IT Eye, disease
(macula, edema; active **salt** forms with **tyrosine kinase** activity)

IT Eye, disease
(macula, senile degeneration; active **salt** forms with **tyrosine kinase** activity)
IT Carcinoma
(mammary; active **salt** forms with **tyrosine kinase** activity)
IT Androgen receptors
Estrogen receptors
Retinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulator; active **salt** forms with **tyrosine kinase** activity)
IT Crystal structure
(of (cyanothiazolylaminopyridinylmethyl)piperazinecarboxylic acid methylamide **salts**)
IT Bone, neoplasm
Sarcoma
(osteosarcoma; active **salt** forms with **tyrosine kinase** activity)
IT Carcinoma
(pulmonary adenocarcinoma; active **salt** forms with **tyrosine kinase** activity)
IT Carcinoma
(pulmonary small-cell; active **salt** forms with **tyrosine kinase** activity)
IT Eye
(retina, vascularization; active **salt** forms with **tyrosine kinase** activity)
IT Eye, disease
(retinal ischemia; active **salt** forms with **tyrosine kinase** activity)
IT Ischemia
(retinal; active **salt** forms with **tyrosine kinase** activity)
IT Lung, neoplasm
(small-cell carcinoma; active **salt** forms with **tyrosine kinase** activity)
IT Troponins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(troponin 1; active **salt** forms with **tyrosine kinase** activity)
IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; active **salt** forms with **tyrosine kinase** activity)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αIIbβ3, antagonists; active **salt** forms with **tyrosine kinase** activity)

IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, agonist; active **salt** forms with **tyrosine kinase** activity)

IT 479611-82-0P 652154-18-2P 652154-19-3P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(active **salt** forms with **tyrosine kinase** activity)

IT 62-56-6, Thiourea, reactions 74-89-5, Methylamine, reactions 1079-66-9 1885-14-9, Phenyl chloroformate 2759-28-6 5327-32-2 19814-75-6 57260-71-6 69194-03-2 69194-04-3 101066-61-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(active **salt** forms with **tyrosine kinase** activity)

IT 6937-03-7P 51640-36-9P 51640-52-9P 54221-95-3P 85989-62-4P 105250-17-7P 161265-03-8P, Xantphos 163361-25-9P 329794-09-4P 329794-13-0P 329794-14-1P 329794-15-2P 479611-85-3P 652154-14-8P 652154-15-9P 652154-16-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(active **salt** forms with **tyrosine kinase** activity)

IT 50-35-1, Thalidomide 10540-29-1, Tamoxifen 33069-62-4, Paclitaxel 37300-21-3, Pentosan polysulfate 84449-90-1, Raloxifene 86090-08-6, Angiostatin 99519-84-3 117048-59-6, Combretastatin A-4 144494-65-5, Tirofiban 148717-90-2, Squalamine 180288-69-1, Trastuzumab 561321-04-8, 6-(O-Chloroacetylcarbonyl)fumagillol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(active **salt** forms with **tyrosine kinase** activity)

IT 127464-60-2, Vascular endothelial growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibodies to; active **salt** forms with **tyrosine kinase** activity)

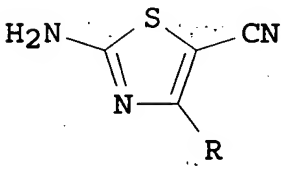
IT 9028-35-7, HMG-CoA reductase 9068-38-6, Reverse transcriptase 39391-18-9, Cyclooxygenase 62229-50-9, Epidermal growth factor 80449-02-1, **Tyrosine kinase** 131384-38-8, Prenyl-protein transferase 141907-41-7, Matrix metalloproteinase 144114-21-6, HIV protease 329900-75-6, COX-2

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor; active **salt** forms with **tyrosine kinase** activity)

L16 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:41160 HCAPLUS
DOCUMENT NUMBER: 140:94038
TITLE: Process for making 2-amino-5-cyanothiazole compounds
INVENTOR(S): **Zhao, Matthew M.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 7 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004010150	A1	20040115	US 2003-607117	20030626
PRIORITY APPLN. INFO.:			US 2002-395922P	P 20020715

OTHER SOURCE(S): CASREACT 140:94038; MARPAT 140:94038
GI



I

AB The present invention relates to methods of prepg. 2-amino-5-cyanothiazoles I [R = H, alkyl, (hetero)aryl], which are useful as intermediates in the prepn. of compds. that are known to be useful in the treatment of cancer and other disease by inhibiting, modulating and/or regulating signal transduction of both

receptor-type and non-receptor type **tyrosine kinases** (no data). The process comprises the steps of: (a) halogenating and hydrolyzing a soln. of an (un)substituted 3-alkoxy or 3-aryloxyacrylonitrile in a solvent, (b) adding thiourea and neutralizing to produce a product, and (c) isolating the aminocyanothiazole I. Thus, brominating and hydrolyzing a soln. of 3-methoxyacrylonitrile in MeCN followed by adding thiourea, and neutralization afforded 75% of 2-amino-5-cyanothiazole.

IC ICM C07D277-18
INCL 548190000
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))

L16 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:855752 HCAPLUS
DOCUMENT NUMBER: 139:354459
TITLE: Solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with **tyrosine kinase** activity
INVENTOR(S): **Karki, Shyam B.**; Payack, Joseph; Treemaneekarn, Varaporn; Wang, Yaling; Sato, Yuichi
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Banyu Pharmaceutical Co., Ltd.
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003088900	A2	20031030	WO 2003-US11022	20030411
WO 2003088900	A3	20040521		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2480325	AA	20031030	CA 2003-2480325	20030411
US 2005113577	A1	20050526	US 2003-506710	20030411
JP 2005528400	T2	20050922	JP 2003-585653	20030411
PRIORITY APPLN. INFO.:			US 2002-372782P P	20020416
			WO 2003-US11022 W	20030411

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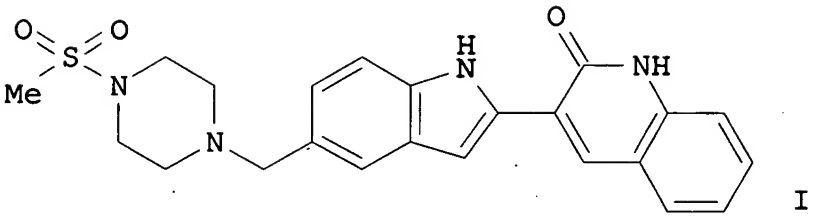

I

AB The present invention relates to solid forms of the I.HCl of which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction, compns. which contain these compds., and methods of using them to treat **tyrosine kinase** -dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. I and its HCl salt were prepd. and crystal forms were obtained and characterized.

IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 27, 28
IT Angiogenesis inhibitors
Antitumor agents
Crystal morphology
Eye, disease
Inflammation
(solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with **tyrosine kinase** activity)
IT 80449-02-1, **Tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with **tyrosine kinase** activity)
IT 415684-58-1P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with **tyrosine kinase** activity)
IT 335649-90-6P, 3-[5-(4-Methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with **tyrosine kinase** activity)
IT 1670-81-1, 1H-Indole-5-carboxylic acid 128676-85-7, 2-Chloro-3-iodoquinoline
RL: RCT (Reactant); RACT (Reactant or reagent)
(solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with **tyrosine kinase** activity)
IT 1075-25-8P, 1H-Indole-5-methanol 335649-83-7P 335649-84-8P 335649-85-9P, 3-Iodo-1H-quinolin-2-one 335649-86-0P 335649-87-1P 335649-88-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with **tyrosine kinase** activity)
IT 335649-89-3P

RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(solid forms of 3-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-1H-quinolin-2-one hydrochloride salt with **tyrosine kinase** activity)

L16 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:117806 HCAPLUS
DOCUMENT NUMBER: 138:153547
TITLE: Preparation of 4-(imidazolyl)-2-pyrimidinamines as **tyrosine kinase** inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Manley, Peter J.; Balitza, Adrienne; Rodman, Leonard; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011836	A1	20030213	WO 2002-US23764	20020726
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004220201	A1	20041104	US 2004-485170	20040129
US 6958340	B2	20051025		

PRIORITY APPLN. INFO.: US 2001-309400P P 20010801

WO 2002-US23764 W 20020726

OTHER SOURCE(S): MARPAT 138:153547

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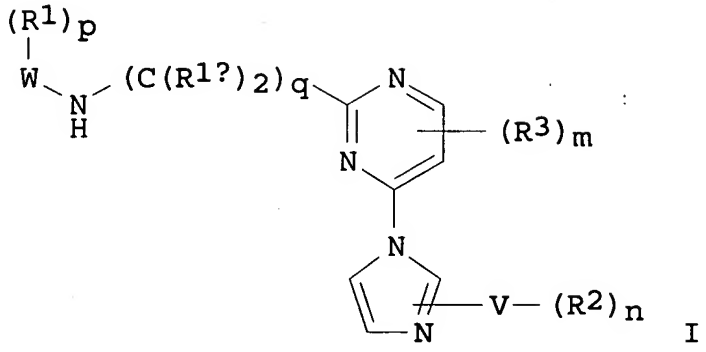

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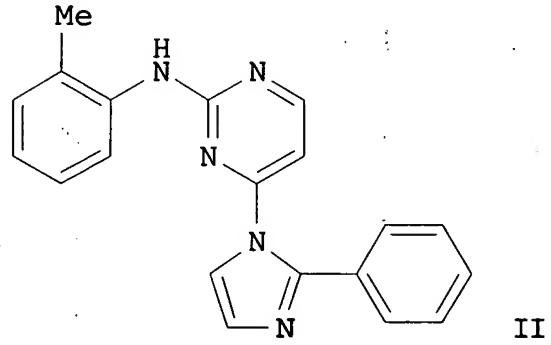


II

AB The present invention relates to title compds. I [wherein R1a = H, (un)substituted alkyl, or OR8, or N(R8)2; R1 and R2 = independently H, halo, CF3, (CH2)tR9COR8, COR9, (CH2)tOR8, CN, (CH2)tNR7R8, (CH2)tCONR7R8, CO2R8, (CH2)tSOq(CH2)tNR7R8, oxido, or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, alkenyl, or alkynyl; R3 = H, CN, halo, N(R8)2, (CH2)tOR8, or (un)substituted

(ar)alkyl or aryl; R7 = independently H or (un)substituted (ar)alkyl; R8 = independently H or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, or aralkyl; or NR7R8 = (un)substituted heterocyclyl; R9 = independently (un)substituted heterocyclyl, alkyl, or aryl; V = bond, aryl, or heterocyclyl; W = aryl or heterocyclyl; m = 0-3; n = 0-6; p = 0-4; q = undefined; t = 0-6; or pharmaceutically acceptable **salts**, hydrates or stereoisomers thereof], which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction, compns. which contain these compds., and methods of using them to treat **tyrosine kinase**-dependent diseases and conditions. For example, 2-phenylimidazole was coupled with 4-chloro-2-(methylthio)pyrimidine in the presence of NaH in DMF and the product oxidized using sodium tungstate dihydrate and H2O2 in EtOAc to give 2-(methylsulfonyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidine. Substitution with 2-methylaniline and purifn. by reverse phase chromatog. afforded II•TFA. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 μM and 5.0 μM. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IC ICM C07D239-28
ICS C07D239-48; A61K031-506; A61P035-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST imidazolyl pyrimidinamine prepn **tyrosine kinase** inhibitor anticancer antiinflammatory; angiogenesis inhibitor imidazolyl pyrimidinamine prepn

IT Troponins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(I, compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(VEGF, compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Lung, neoplasm
(adenocarcinoma; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibody, compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase**

inhibitors)
IT Meningitis
(bacterial; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blocker, compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Antitumor agents
(brain; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Mammary gland, neoplasm
(carcinoma; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Ischemia
(cerebral; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Radiotherapy
(combination therapy with anticancer agents; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Angiogenesis inhibitors
Cytotoxic agents
(compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Androgen receptors
Estrogen receptors
Retinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Interleukin 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Dermatitis
(contact; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Allergy
(delayed hypersensitivity; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Eye, disease
(diabetic retinopathy; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)
IT Growth factors, animal

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fibroblast-derived growth factors, inhibitor, compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Antitumor agents
Neuroglia, neoplasm
(glioblastoma; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Lymphoma
(histiocytic; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Epidermal growth factor receptors
Platelet-derived growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor, compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Brain, disease
(ischemia; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Antitumor agents
(larynx tumor inhibitors; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Antitumor agents
(lung; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Eye, disease
(macula, degeneration; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Carcinoma
(mammary; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Urogenital system
(neoplasm; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Angiogenesis
(neovascularization, retinal; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Antitumor agents
Bone, neoplasm
Sarcoma
(osteosarcoma; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Allergy inhibitors

Angiogenesis
Angiogenesis inhibitors
Anti-inflammatory agents
Antiarthritics
Antirheumatic agents
Antitumor agents
Bone, disease
Brain, neoplasm
Eye, disease
Human
Inflammation
Larynx, neoplasm
Lung, neoplasm
Lymphatic system
Osteoarthritis
Pancreas, neoplasm
Preeclampsia
Psoriasis
Rheumatoid arthritis
Rickets
Signal transduction, biological
Stomach, neoplasm
Wound healing promoters
(prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Epidermal growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Carcinoma
(pulmonary adenocarcinoma; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Carcinoma
(pulmonary small-cell; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Eye, disease
(retina, neovascularization; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Lung, neoplasm
(small-cell carcinoma; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Antitumor agents
(stomach; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (type VEGFR-2; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (α, compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (αIIbβ3, antagonist, compn. component; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT 9028-35-7, HMG-CoA reductase 9068-38-6, Reverse transcriptase 39391-18-9, Cyclooxygenase 80449-02-1, **Tyrosine kinase** 131384-38-8, Prenyltransferase 141907-41-7, Matrix metalloproteinase 144114-21-6, HIV protease 329900-75-6, COX 2
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT 13570-00-8P, 3-(1H-Imidazol-2-yl)pyridine 31722-49-3P, 1H-Imidazole-2-carbonitrile 89532-38-7P, 2-Cyclopropyl-1H-imidazole 127020-07-9P 314061-27-3P, 1-Acetyl-4-(3-nitrobenzyl)piperazine 496794-78-6P, 2-(Methylsulfonyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidine 496795-17-6P, 3-[[(tert-Butyldimethylsilyl)oxy]methyl]-5-methylaniline 496795-19-8P, tert-Butyl [3-(hydroxymethyl)-5-methylphenyl]carbamate 496795-20-1P, tert-Butyl (3-formyl-5-methylphenyl)carbamate 496795-22-3P, tert-Butyl [3-[(4-acetylpiperazin-1-yl)methyl]-5-methylphenyl]carbamate 496795-23-4P, 3-[(4-Acetylpiperazin-1-yl)methyl]-5-methylaniline 496795-38-1P, 2-Chloro-4-(2-phenyl-1H-imidazol-1-yl)pyrimidine 496795-47-2P, 5-(1H-Imidazol-2-yl)pyrimidine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT 141349-89-5, Src kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT 99-61-6, 3-Nitrobenzaldehyde 108-69-0, 3,5-Dimethylaniline 349-55-3, 3-Methoxy-5-trifluoromethylaniline 462-08-8, 3-Aminopyridine 500-22-1, Pyridine-3-carboxaldehyde 504-29-0,

2-Aminopyridine 670-96-2, 2-Phenylimidazole 768-35-4, 3-Fluorophenylboronic acid 1489-69-6, Cyclopropylcarboxaldehyde 3934-20-1, 2,4-Dichloropyrimidine 5751-20-2, 2-(Methylthio)pyrimidin-4(3H)-one 10070-92-5, Pyrimidine-5-carboxaldehyde 10111-08-7, Imidazole-2-carboxaldehyde 13889-98-0, 1-Acetylpiperazine 18162-48-6, tert-Butyldimethylsilyl chloride 24424-99-5 49844-90-8, 4-Chloro-2-(methylthio)pyrimidine 146335-25-3, (3-Amino-5-methylphenyl)methanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT 50-35-1, Thalidomide 10540-29-1, Tamoxifen 33069-62-4, Paclitaxel 84449-90-1, Raloxifene 86090-08-6, Angiostatin 99519-84-3, CAI 117048-59-6, Combretastatin A-4 132746-81-7, 6-O-(N-Chloroacetylcarbamoyl)fumagillol 140207-92-7 144494-65-5, Tirofiban 148717-90-2, Squalamine 180288-69-1, Trastuzumab
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT 496795-37-0P, 4-(2-Phenyl-1H-imidazol-1-yl)-N-(pyridin-3-yl)pyrimidin-2-amine 496795-62-1P, 4-(2-Chloro-1H-imidazol-1-yl)-N-(3,5-dimethylphenyl)pyrimidin-2-amine
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**tyrosine kinase** inhibitor; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

IT 496794-79-7P, N-(2-Methylphenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-80-0P 496794-82-2P, N-(2-Methoxyphenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-83-3P 496794-84-4P, N-(2-Fluorophenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-85-5P 496794-86-6P, N-(3-Chlorophenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-87-7P 496794-88-8P, N-(3,5-Dichlorophenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-89-9P 496794-90-2P, N-(3-Fluorophenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-91-3P 496794-92-4P, N-(3-Methoxyphenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-93-5P 496794-94-6P, N-(3-Methylphenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-95-7P 496794-96-8P, N-(3,5-Dimethoxyphenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-97-9P 496794-98-0P, N-(4-Chlorophenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496794-99-1P 496795-00-7P, N-(4-Fluorophenyl)-4-(2-phenyl-1H-

imidazol-1-yl)pyrimidin-2-amine 496795-01-8P 496795-02-9P, N-(4-Methoxyphenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-03-0P 496795-04-1P, N-(4-Methylphenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-05-2P 496795-06-3P, N-[3,5-Bis(trifluoromethyl)phenyl]-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-07-4P 496795-08-5P, N-[3-Methyl-5-(trifluoromethyl)phenyl]-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-09-6P 496795-10-9P, N-(3,5-Difluorophenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-11-0P 496795-12-1P, 4-(2-Phenyl-1H-imidazol-1-yl)-N-[3-(trifluoromethyl)phenyl]pyrimidin-2-amine 496795-13-2P 496795-14-3P, N-[3-Methoxy-5-(trifluoromethyl)phenyl]-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-15-4P, [3-Methyl-5-[[4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-yl]amino]phenyl]methanol 496795-16-5P 496795-18-7P, N-[3-[(4-Acetylpiperazin-1-yl)methyl]-5-methylphenyl]-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-24-5P, N-(3,5-Dimethylphenyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-25-6P, 4-(2-Phenyl-1H-imidazol-1-yl)-N-(pyridin-4-yl)pyrimidin-2-amine 496795-26-7P, 4-(2-Phenyl-1H-imidazol-1-yl)-N-(pyrimidin-4-yl)pyrimidin-2-amine 496795-27-8P, 4-(2-Phenyl-1H-imidazol-1-yl)-N-(pyrimidin-2-yl)pyrimidin-2-amine 496795-28-9P, 4-(2-Phenyl-1H-imidazol-1-yl)-N-(pyrazin-2-yl)pyrimidin-2-amine 496795-29-0P, 4-(2-Phenyl-1H-imidazol-1-yl)-N-(1,3,4-thiadiazol-2-yl)pyrimidin-2-amine 496795-30-3P, N-(5-Methyl-1,3,4-thiadiazol-2-yl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-31-4P, N-(Isoxazol-3-yl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-32-5P, N-(3-Methylisoxazol-5-yl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-33-6P, N-(4-Methyl-1,3-thiazol-2-yl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-34-7P, N-(2-Methylpyridin-4-yl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-35-8P, N-(2,6-Dimethylpyridin-4-yl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-36-9P, 4-(2-Phenyl-1H-imidazol-1-yl)-N-(pyridin-2-yl)pyrimidin-2-amine 496795-40-5P, N-(1-Oxidopyridin-3-yl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-42-7P, N-(3,5-Dimethylphenyl)-4-[2-(pyridin-2-yl)-1H-imidazol-1-yl]pyrimidin-2-amine 496795-44-9P, N-(3,5-Dimethylphenyl)-4-[2-(pyrimidin-5-yl)-1H-imidazol-1-yl]pyrimidin-2-amine 496795-45-0P 496795-48-3P, N-(3,5-Dimethylphenyl)-4-[2-(pyridin-3-yl)-1H-imidazol-1-yl]pyrimidin-2-amine 496795-51-8P, 4-(2-Cyclopropyl-1H-imidazol-1-yl)-N-(3,5-dimethylphenyl)pyrimidin-2-amine 496795-52-9P 496795-55-2P, N-(3,5-Dimethylphenyl)-4-(4-methyl-2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-56-3P 496795-57-4P, 1-[2-[(3,5-Dimethylphenyl)amino]pyrimidin-4-yl]-1H-imidazole-2-

carbonitrile 496795-58-5P, N-(3,5-Dimethylphenyl)-4-(2-methyl-1H-imidazol-1-yl)pyrimidin-2-amine 496795-59-6P 496795-60-9P, 4-(2-Amino-1H-imidazol-1-yl)-N-(3,5-dimethylphenyl)pyrimidin-2-amine 496795-61-0P 496795-63-2P, N-(3,5-Dimethylphenyl)-4-[2-(3-fluorophenyl)-1H-imidazol-1-yl]pyrimidin-2-amine 496795-64-3P 496795-65-4P, N-[3-[(4-Acetylpiperazin-1-yl)methyl]phenyl]-4-(2-phenyl-1H-imidazol-1-yl)pyrimidin-2-amine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**tyrosine kinase** inhibitor; prepn. of (imidazolyl)pyrimidinamines as **tyrosine kinase** inhibitors)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:97306 HCAPLUS
DOCUMENT NUMBER: 138:137303
TITLE: Preparation of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Manley, Peter J.; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003009852	A1	20030206	WO 2002-US23191	20020719

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

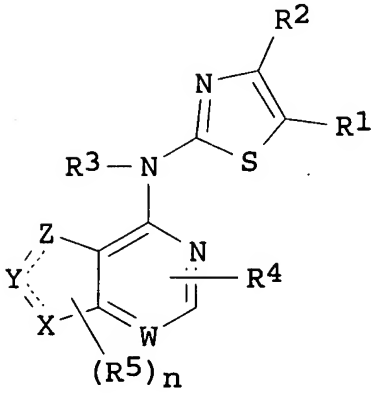
US 2004235867 A1 20041125 US 2004-484986 200401 23

PRIORITY APPLN. INFO.: US 2001-307443P P 200107 24

WO 2002-US23191 W 200207 19

OTHER SOURCE(S): MARPAT 138:137303

GI



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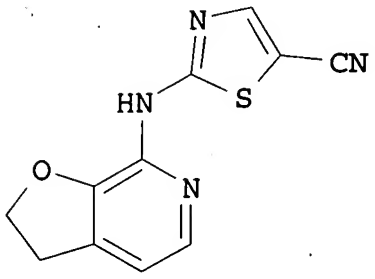

II

AB The present invention relates to the prepn. of title compds. I [wherein X, Y, and Z = C, S, N, or O, provided that at least one of X, Y, or Z = C; W = C or N; n = 0-6; R1, R2, and R4 = independently H, perfluoroalkyl(oxy), OH, CN, halo, or (un)substituted (CO)rOs-alkyl, (CO)rOs-alkenyl, (CO)rOs-alkynyl, (CO)rOs-aryl, (CO)rOs-heterocyclyl, or alkyl-NRaRb; R3 = H, SO2Rc, (CO)rRc, or CO2Rc; R5 = R3 or Or(CO)sNRaRb, halo, OH, oxo, perfluoroalkyl(oxy), CHO, CO2H, CN, or (un)substituted (CO)rOs-aryl, (CO)rOs-

heterocyclyl, or (CO)rOs-alkyl; r = 0-1; s = 0-1; Ra and Rb = independently H, SO2Rc, CO2Rc, or (un)substituted (CO)r-alkyl, (CO)r-heterocyclyl, or (CO)r-aryl; or NRaRb = (un)substituted monocyclic or bicyclic heterocycle; Rc = (un)substituted alkyl, aryl, benzyl, or heterocyclyl; or pharmaceutically acceptable **salts** or stereoisomers thereof], which inhibit, regulate, and/or modulate **tyrosine kinase** signal transduction, compns. which contain these compds., and methods of using them to treat **tyrosine kinase**-dependent diseases and conditions. For example, 7-bromofuro[2,3-c]pyridine was converted to the amine using benzophenone imine, NaOBu-t, racemic BINAP, and Pd2(dba)3 in dry toluene and then hydrogenated with 10% Pd/C in AcOH to give 2,3-dihydrofuro[2,3-c]pyridin-7-amine. Addn. of 2-chloro-5-cyanothiazole in the presence of NaH in THF afforded the (furopyridinylamino)thiazolecarbonitrile II. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001 μM and 5.0 μM. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IC ICM A61K031-52
ICS A61K031-519; A61K031-437; A61K031-4355; A61K031-4365; A61K031-496; C07D473-34; C07D487-04; C07D491-048; C07D497-04; C07D498-04; C07D471-04; C07D515-02

CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST heterocyclylamino thiazolecarbonitrile prepn **tyrosine kinase** inhibitor; angiogenisis inhibitor heterocyclylamino thiazolecarbonitrile prepn

IT Troponins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(I, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Antibodies and Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(VEGF, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Lung, neoplasm
(adenocarcinoma; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Vascular endothelial growth factor receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibody, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Meningitis
(bacterial; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blocker, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Antitumor agents
(brain; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Mammary gland, neoplasm
(carcinoma; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Ischemia
(cerebral; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Radiotherapy
(combination therapy with anticancer agents; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Angiogenesis inhibitors
Cytotoxic agents
(compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Androgen receptors
Estrogen receptors
Retinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Interleukin 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase**

inhibitors)
IT Dermatitis
(contact; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Allergy
(delayed hypersensitivity; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Eye, disease
(diabetic retinopathy; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Growth factors, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fibroblast-derived growth factors, inhibitor, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Antitumor agents
Neuroglia, neoplasm
(glioblastoma; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Lymphoma
(histiocytic; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Epidermal growth factor receptors
Platelet-derived growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Brain, disease
(ischemia; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Antitumor agents
(larynx tumor inhibitors; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Antitumor agents
(lung; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase**

inhibitors)
IT Eye, disease
(macula, degeneration; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Carcinoma
(mammary; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Urogenital system
(neoplasm; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Angiogenesis
(neovascularization, retinal; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Antitumor agents
Bone, neoplasm
Sarcoma
(osteosarcoma; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)
IT Allergy inhibitors
Angiogenesis
Angiogenesis inhibitors
Anti-inflammatory agents
Antiarthritics
Antirheumatic agents
Antitumor agents
Bone, disease
Brain, neoplasm
Eye, disease
Human
Inflammation
Larynx, neoplasm
Lung, neoplasm
Lymphatic system
Osteoarthritis
Pancreas, neoplasm
Preeclampsia
Psoriasis
Rheumatoid arthritis
Rickets
Stomach, neoplasm

Wound healing promoters
(prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Carcinoma
(pulmonary adenocarcinoma; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Carcinoma
(pulmonary small-cell; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Eye, disease
(retina, neovascularization; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Lung, neoplasm
(small-cell carcinoma; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Antitumor agents
(stomach; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αIIbβ3, antagonist, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT 50-35-1, Thalidomide 10540-29-1, Tamoxifen 33069-62-4, Paclitaxel 84449-90-1, Raloxifene 86090-08-6, Angiostatin 99519-84-3, CAI 117048-59-6, Combretastatin A-4 132746-81-7, 6-O-(N-Chloroacetylcarbamoyl)fumagillol 140207-92-7 144494-65-5, Tirofiban 148717-90-2, Squalamine 180288-69-1, Trastuzumab
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT 9028-35-7, HMG-CoA reductase 9068-38-6, Reverse transcriptase 39391-18-9, Cyclooxygenase 80449-02-1, **Tyrosine**

kinase 131384-38-8, Prenyltransferase 141907-41-7, Matrix metalloproteinase 144114-21-6, HIV protease 329900-75-6, COX 2
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor, compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT 33007-09-9P, Furo[3,2-c]pyridin-4-amine 60290-21-3P, 4-Chloro-1H-pyrrolo[3,2-c]pyridine 117332-47-5P 190001-40-2P, tert-Butyl 4-(chloroacetyl)piperazine-1-carboxylate 215453-35-3P, Thieno[3,2-c]pyridin-4-amine 234108-73-7P 494767-14-5P, 2,3-Dihydrofuro[2,3-c]pyridin-7-amine 494767-17-8P, 2-[[3-[[(tert-Butyldimethylsilyl)oxy]methyl]-2,3-dihydrofuro[2,3-c]pyridin-7-yl]amino]-1,3-thiazole-5-carbonitrile 494767-19-0P, 1-Methyl-1H-pyrazolo[4,3-c]pyridin-4-amine 494767-21-4P, tert-Butyl 2-chloro-3-(2-hydroxyethyl)pyridin-4-ylcarbamate 494767-22-5P, tert-Butyl 4-chloro-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxylate 494767-23-6P, tert-Butyl 4-amino-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxylate 494767-24-7P 494767-29-2P, 4-Chloro-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine 494767-30-5P, 4-Chloro-N,N-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxamide 494767-31-6P, 4-Amino-N,N-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxamide 494767-37-2P, 2-(4-Chloro-1H-pyrrolo[3,2-c]pyridin-1-yl)-N,N-diethylacetamide 494767-38-3P, 2-(4-Chloro-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-1-yl)-N,N-diethylacetamide 494767-39-4P, 2-(4-Amino-1H-pyrrolo[3,2-c]pyridin-1-yl)-N,N-diethylacetamide 494767-41-8P, Methyl (4-chloro-1H-pyrrolo[3,2-c]pyridin-1-yl)acetate 494767-42-9P, 2-(4-Chloro-1H-pyrrolo[3,2-c]pyridin-1-yl)-N,N-dimethylacetamide 494767-43-0P, 2-(4-Amino-1H-pyrrolo[3,2-c]pyridin-1-yl)-N,N-dimethylacetamide 494767-46-3P, tert-Butyl 4-[(4-chloro-1H-pyrrolo[3,2-c]pyridin-1-yl)acetyl]piperazine-1-carboxylate 494767-47-4P, tert-Butyl 4-[[4-[(5-cyano-1,3-thiazol-2-yl)amino]-1H-pyrrolo[3,2-c]pyridin-1-yl]acetyl]piperazine-1-carboxylate 494767-49-6P 494767-51-0P 494767-53-2P, 2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N,N-diethylacetamide 494767-55-4P, 4,6-Dichloro-5-(2-chloroethyl)pyrimidine 494767-56-5P, 2-(4-Chloro-5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N,N-dimethylacetamide 494767-57-6P, 2-(4-Amino-5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N,N-dimethylacetamide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT 96-32-2, Methyl bromoacetate 1857-19-8 2315-36-8, N,N-Diethyl-2-chloroacetamide 3680-69-1, 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine 14080-56-9, Thieno[2,3-d]pyrimidin-4-amine 14432-12-3, 4-Amino-2-chloropyridine 18162-48-6, tert-Butyldimethylsilyl chloride 19406-00-9, Methyl 2-oxotetrahydrofuran-3-carboxylate 24424-99-5, Di-tert-butyldi-carbonate 27685-94-5, 4-Chlorothieno[3,2-c]pyridine 31270-80-1, 4-Chlorofuro[3,2-c]pyridine 51640-36-9, 2-Chloro-5-cyanothiazole 51640-52-9, 2-Amino-5-cyanothiazole 57260-71-6, tert-Butyl piperazine-1-carboxylate 71703-04-3, 4-Amino-1-methyl-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one 174469-04-6, (7-Chloro-2,3-dihydrofuro[2,3-c]pyridin-3-yl)methanol 266353-32-6, 4-Nitronicotinaldehyde 1-oxide 494767-15-6, 7-Bromofuro[2,3-c]pyridine
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT 494767-20-3P, 2-[(2,3-Dihydro-1H-pyrrolo[3,2-c]pyridin-4-yl)amino]-1,3-thiazole-5-carbonitrile
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**tyrosine kinase** inhibitor; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

IT 494767-13-4P, 2-[(2,3-Dihydrofuro[2,3-c]pyridin-7-yl)amino]-1,3-thiazole-5-carbonitrile 494767-16-7P, 2-[[3-(Hydroxymethyl)-2,3-dihydrofuro[2,3-c]pyridin-7-yl]amino]-1,3-thiazole-5-carbonitrile 494767-18-9P, 2-[(1-Methyl-1H-pyrazolo[4,3-c]pyridin-4-yl)amino]-1,3-thiazole-5-carbonitrile 494767-25-8P, 2-[(1H-Pyrrolo[3,2-c]pyridin-4-yl)amino]-1,3-thiazole-5-carbonitrile 494767-26-9P, 2-[[1-(Methylsulfonyl)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-4-yl]amino]-1,3-thiazole-5-carbonitrile 494767-27-0P 494767-28-1P, 4-[(5-Cyano-1,3-thiazol-2-yl)amino]-N,N-dimethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine-1-carboxamide 494767-32-7P, 2-[(1-Methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-c]pyridin-4-yl)amino]-1,3-thiazole-5-carbonitrile 494767-33-8P, 2-[(Thieno[3,2-c]pyridin-4-yl)amino]-1,3-thiazole-5-carbonitrile 494767-34-9P, 2-[(Furo[3,2-c]pyridin-4-yl)amino]-1,3-thiazole-5-carbonitrile 494767-35-0P, 2-[(Thieno[2,3-d]pyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile 494767-36-1P, 2-[4-[(5-Cyano-1,3-thiazol-2-yl)amino]-1H-pyrrolo[3,2-c]pyridin-1-yl]-N,N-diethylacetamide 494767-40-7P, 2-[4-[(5-Cyano-1,3-thiazol-2-yl)amino]-1H-pyrrolo[3,2-c]pyridin-1-yl]-N,N-dimethylacetamide 494767-44-1P, 2-[[1-[2-Oxo-2-(piperazin-

1-yl)ethyl]-1H-pyrrolo[3,2-c]pyridin-4-yl]amino]-1,3-thiazole-5-carbonitrile 494767-45-2P 494767-48-5P, 2-[3-Chloro-4-[(5-cyano-1,3-thiazol-2-yl)amino]-1H-pyrrolo[3,2-c]pyridin-1-yl]-N,N-dimethylacetamide 494767-50-9P, 2-[2,3-Dichloro-4-[(5-cyano-1,3-thiazol-2-yl)amino]-1H-pyrrolo[3,2-c]pyridin-1-yl]-N,N-dimethylacetamide 494767-52-1P, 2-[4-[(5-Cyano-1,3-thiazol-2-yl)amino]-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N,N-diethylacetamide 494767-54-3P, 2-[4-[(5-Cyano-1,3-thiazol-2-yl)amino]-5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidin-7-yl]-N,N-dimethylacetamide
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**tyrosine kinase** inhibitor; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as **tyrosine kinase** inhibitors)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:314903 HCAPLUS
DOCUMENT NUMBER: 136:325437
TITLE: Preparation of oxoquinolinylindole-5-methanamine salts as **tyrosine kinase** signal transduction modulators
INVENTOR(S): Fraley, Mark E.; **Karki, Shyam B.**; Kim, Yuntae
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032861	A2	20020425	WO 2001-US32508	20011017
WO 2002032861	A3	20020815		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2424689	AA	20020425	CA 2001-2424689	20011017
AU 2002026877	A5	20020429	AU 2002-26877	20011017
US 2002072526	A1	20020613	US 2001-981979	20011017
US 6656942	B2	20031202		
EP 1328519	A2	20030723	EP 2001-987742	20011017
EP 1328519	B1	20050907		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004511541	T2	20040415	JP 2002-536045	20011017
AT 303998	E	20050915	AT 2001-987742	20011017
US 2004002501	A1	20040101	US 2003-398851	20030410
US 6960590	B2	20051101		
PRIORITY APPLN. INFO.:			US 2000-241043P P	20001017
			WO 2001-US32508 W	20011017

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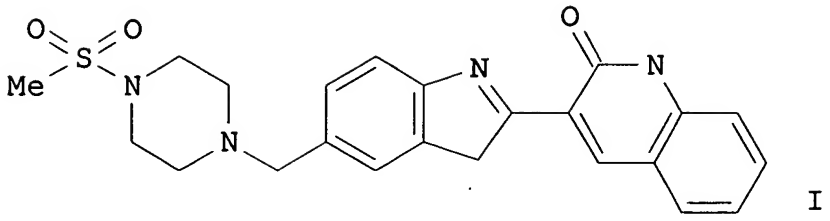

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AB Title compds. were prepd. as **tyrosine kinase** signal transduction modulators (no data). Thus, di-protected 5-hydroxymethylindole-2-boronic acid was condensed with 3-iodo-2-quinolinone (prepn. each given) and the O-deprotected product oxidized to the aldehyde which was reductively aminated by 1-methanesulfonylpiperazine to give, after deprotection and salt formation, title compd. I.MeSO3H.

IC ICM C07D

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

ST oxoquinolinylindolemethanamine salt **tyrosine kinase** signal transduction modulator

IT Antitumor agents
Signal transduction, biological
(prepn. of oxoquinolinylindole-5-methanamine salts as **tyrosine kinase** signal transduction modulators)

IT 335649-90-6P 335649-93-9P 335649-95-1P 408502-06-7P
415684-56-9P 415684-57-0P 415684-58-1P 415684-59-2P
415684-60-5P 415684-61-6P 415684-62-7P 415684-63-8P
415684-64-9P 415684-65-0P 415684-66-1P 415684-68-3P
415684-69-4P 415684-70-7P 415684-71-8P 415684-72-9P
415684-73-0P 415684-74-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of oxoquinolinylindole-5-methanamine salts as **tyrosine kinase** signal transduction modulators)

IT 1670-81-1, 1H-Indole-5-carboxylic acid 1953-54-4, 1H-Indol-5-ol
18162-48-6, tert-Butyldimethylsilyl chloride 97994-45-1
117701-75-4 128676-84-6 415684-75-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of oxoquinolinylindole-5-methanamine salts as **tyrosine kinase** signal transduction modulators)

IT 1075-25-8P, 1H-Indole-5-methanol 106792-38-5P 128676-85-7P
335649-60-0P 335649-61-1P 335649-62-2P 335649-63-3P

335649-83-7P 335649-84-8P 335649-85-9P 335649-87-1P
335649-88-2P 335649-89-3P 415684-67-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of oxoquinolinylindole-5-methanamine salts as **tyrosine kinase** signal transduction modulators)

L16 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:300706 HCAPLUS
DOCUMENT NUMBER: 134:326411
TITLE: Preparation of 3-(2-indolyl)quinoline-2-one derivatives as **tyrosine kinase** inhibitors
INVENTOR(S): Arrington, Kenneth L.; **Bilodeau, Mark T.**; Fraley, Mark E.; Hartman, George D.; Hoffman, William F.; Hungate, Randall W.; Kim, Yuntae
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001029025	A2	20010426	WO 2000-US28625	20001016
WO 2001029025	A3	20011101		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2387351	AA	20010426	CA 2000-2387351	20001016
BR 2000014843	A	20020611	BR 2000-14843	

				200010 16
EP 1226136	A2	20020731	EP 2000-978230	
				200010 16
EP 1226136	B1	20041229		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
TR 200201051	T2	20020923	TR 2002-200201051	
				200010 16
JP 2003512369	T2	20030402	JP 2001-531825	
				200010 16
EE 200200201	A	20030616	EE 2002-201	
				200010 16
NZ 518001	A	20040528	NZ 2000-518001	
				200010 16
AU 778588	B2	20041209	AU 2001-15710	
				200010 16
AT 286045	E	20050115	AT 2000-978230	
				200010 16
PT 1226136	T	20050429	PT 2000-978230	
				200010 16
ES 2234698	T3	20050701	ES 2000-978230	
				200010 16
US 6306874	B1	20011023	US 2000-690598	
				200010 17
ZA 2002002985	A	20030416	ZA 2002-2985	
				200204 16
NO 2002001820	A	20020523	NO 2002-1820	
				200204 18
US 6794393	B1	20040921	US 2002-110872	
				200204 18
BG 106710	A	20030331	BG 2002-106710	

US 2005096344 A1 20050505 US 2004-900662 20040728

PRIORITY APPLN. INFO.: US 1999-160356P P 19991019

WO 2000-US28625 W 20000016

US 2002-110872 A1 20020418

OTHER SOURCE(S): MARPAT 134:326411

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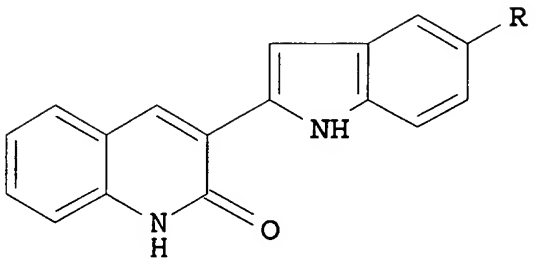

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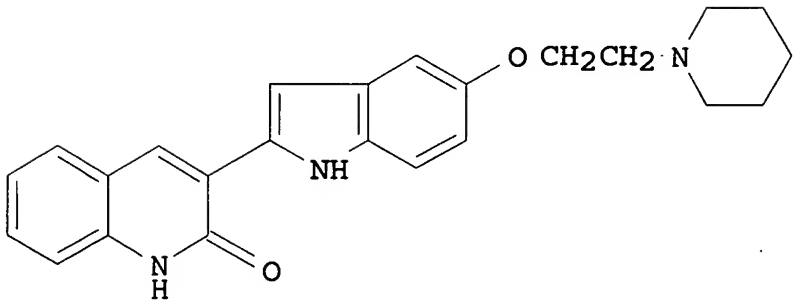

II

AB Title compds. [I; R = (CH3)2NCH2CH(CH3)CH2O,

(CH3OCH2CH2)(C6H5CH2)NCH2CH2O, (CH3CH2)2NCH2CH2O, (CH3)(C6H5CH2)NCH2CH2CH2O, (CH3OCH2CH2)(HOOCCH2CH2)NCH2CH2O, (CH3OCH2CH2)(CH3SO2)NCH2, cycloalkylaminoalkyl, heterocyclylalkyl, etc.], stereoisomer, and pharmaceutically acceptable **salts** are prepd. and inhibit, regulate and/or modulate **tyrosine kinase** signal transduction. Title compds. are tested on VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001-5.0 μM. Pharmaceutical compns. and methods of using them to treat **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, etc. are discussed. Thus, the title compd. II was prepd.

IC ICM C07D401-00

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

ST indolylquinolineone prepn **tyrosine kinase** inhibitor

IT Dermatitis
(contact; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT Allergy
(delayed hypersensitivity; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT Eye, disease
(diabetic retinopathy; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT Brain, disease
(ischemia; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors in reducing or preventing tissue damage)

IT Eye, disease
(macula, senile degeneration; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT Bone, neoplasm
(osteosarcoma; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT Pentosans
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polysulfate; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors in compn. with other agents)

IT Angiogenesis
Osteoarthritis
Psoriasis

Rickets
(prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT Interleukin 12
Troponins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors in compn. with other agents)

IT Radiotherapy
(prepn. of 3-(2-indolyl)quinolineone derivs. as **tyrosine kinase** inhibitors in compn. with other treatment)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors in compn. with other agents)

IT Integrins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(αIIb; prepn. of 3-(2-indolyl)quinolineone derivs. as **tyrosine kinase** inhibitors in compn. with antagonist)

IT Integrins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β3; prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors in compn. with other agents)

IT 80449-02-1, **Tyrosine kinase**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT 335649-64-4P 335649-65-5P 335649-66-6P 335649-67-7P
335649-68-8P 335649-69-9P 335649-70-2P 335649-71-3P
335649-72-4P 335649-73-5P 335649-74-6P 335649-76-8P
335649-80-4P 335649-82-6P 335649-91-7P 335649-92-8P
335649-93-9P 335649-94-0P 335649-95-1P 335649-96-2P
335649-97-3P 335649-98-4P 335649-99-5P 335650-00-5P
335650-01-6P 335650-03-8P 335650-04-9P 335650-07-2P
335650-08-3P 335650-14-1P 335650-16-3P 335650-22-1P
335650-23-2P 335650-26-5P 335650-27-6P 335650-28-7P
335650-29-8P 335650-30-1P 335650-31-2P 335650-33-4P

335650-35-6P 335650-36-7P 335650-37-8P 335650-38-9P
335650-39-0P 335650-40-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT 110-91-8, Morpholine, reactions 121-43-7, Trimethylborate 1075-25-8, 1H-Indole-5-methanol 1670-81-1, 1H-Indole-5-carboxylic acid 1953-54-4, 5-Hydroxyindole 2008-75-5, 1-(2-Chloroethyl)-piperidine hydrochloride 7693-46-1, 4-Nitrophenyl chloroformate 13504-85-3 55276-43-2 57260-71-6, tert-Butyl 1-piperazine carboxylate 73874-95-0, tert-Butyl 4-piperidinylcarbamate 84358-13-4 90905-32-1 128676-84-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT 18162-48-6P, tert-Butyldimethylsilyl chloride 96522-37-1P 106792-38-5P 128676-85-7P, 2-Chloro-3-iodo-quinoline 335649-60-0P 335649-61-1P 335649-62-2P 335649-63-3P 335649-75-7P 335649-77-9P 335649-78-0P 335649-79-1P 335649-81-5P 335649-83-7P 335649-84-8P 335649-85-9P 335649-86-0P 335649-87-1P 335649-88-2P 335649-89-3P 335649-90-6P 335650-05-0P 335650-06-1P 335650-09-4P 335650-10-7P 335650-11-8P 335650-12-9P 335650-13-0P 335650-15-2P 335650-17-4P 335650-18-5P 335650-19-6P 335650-21-0P 335650-24-3P 335650-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors)

IT 50-35-1, Thalidomide 10540-29-1, Tamoxifen 84449-90-1, Raloxifene 86090-08-6, Angiostatin 108102-51-8D, Fumagillol, 6-o-chloroacetylcarbonyl deriv. 117048-59-6, Combretastatin A-4 148717-90-2, Squalamine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of 3-(2-indolyl)quinoline-2-one derivs. as **tyrosine kinase** inhibitors in compn. with other agents)

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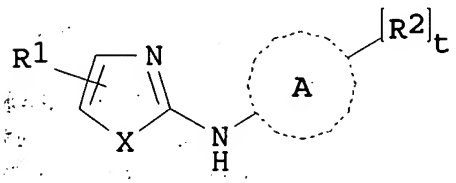
L17 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1103347 HCAPLUS
DOCUMENT NUMBER: 143:387019
TITLE: Preparation of thiazole **tyrosine kinase** inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Rodman, Leonard
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 30 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005228031	A1	20051013	US 2004-823156	20040413

PRIORITY APPLN. INFO.: US 2004-823156 20040413

OTHER SOURCE(S): MARPAT 143:387019
GI



I

AB The title compds. I [A = (hetero)aryl; X = S, O; R1 = (un)substituted Ph, CN, (un)substituted amido; R2 = H, CN, halo, etc.; t = 0-3] which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction, and are useful for treating **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals, were

prepd. Thus, reacting (1-bromo-2,2-dimethoxyethyl)benzene with Ph thiourea afforded N,5-diphenyl-1,3-thiazol-2-amine. The compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001-5.0 μM. The pharmaceutical compn. s comprising the compds. I alone or in combination with other therapeutic agents, are disclosed.

IC ICM A61K031-426
ICS C07D277-18
INCL 514370000; 548190000
CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
ST thiazole prepn VEGF **tyrosine kinase** inhibitor
IT Lung, neoplasm
(adenocarcinoma, treating; prepn. of thiazole **tyrosine kinase** inhibitors)
IT Mammary gland, neoplasm
(carcinoma, treating; prepn. of thiazole **tyrosine kinase** inhibitors)
IT Eye, disease
(diabetic retinopathy, treating; prepn. of thiazole **tyrosine kinase** inhibitors)
IT Neuroglia, neoplasm
(glioblastoma, treating; prepn. of thiazole **tyrosine kinase** inhibitors)
IT Eye, disease
(macula, degeneration, treating; prepn. of thiazole **tyrosine kinase** inhibitors)
IT Carcinoma
(mammary, treating; prepn. of thiazole **tyrosine kinase** inhibitors)
IT Angiogenesis
(neovascularization, retinal, treating; prepn. of thiazole **tyrosine kinase** inhibitors)
IT Human
Signal transduction, biological
(prepn. of thiazole for modulating **tyrosine kinase** signal transduction)
IT Angiogenesis
Angiogenesis inhibitors
Antitumor agents
Combination chemotherapy
(prepn. of thiazole **tyrosine kinase** inhibitors)
IT Carcinoma
(pulmonary adenocarcinoma, treating; prepn. of thiazole

tyrosine kinase inhibitors)

IT Carcinoma
(pulmonary small-cell, treating; prepn. of thiazole **tyrosine kinase** inhibitors)

IT Eye, disease
(retina, neovascularization, treating; prepn. of thiazole **tyrosine kinase** inhibitors)

IT Lung, neoplasm
(small-cell carcinoma, treating; prepn. of thiazole **tyrosine kinase** inhibitors)

IT Urogenital system, disease
(treating cancer of genitourinary tract; prepn. of thiazole **tyrosine kinase** inhibitors)

IT Atherosclerosis
(treating; prepn. of thiazole for modulating **tyrosine kinase** signal transduction)

IT Brain, neoplasm
Larynx, neoplasm
Lung, neoplasm
Lymphatic system, neoplasm
Lymphoma
Neoplasm
Pancreas, neoplasm
Stomach, neoplasm
(treating; prepn. of thiazole **tyrosine kinase** inhibitors)

IT 33069-62-4, Paclitaxel 144494-65-5, Tirofiban 180288-69-1, Trastuzumab
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; prepn. of thiazole **tyrosine kinase** inhibitors)

IT 127464-60-2, VEGF
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of thiazole for modulating **tyrosine kinase** signal transduction)

IT 133972-64-2P 866756-90-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of thiazole **tyrosine kinase** inhibitors)

IT 135307-33-4P 306321-46-0P 681002-66-4P 716317-92-9P
716317-93-0P 866756-61-8P 866756-62-9P 866756-63-0P
866756-64-1P 866756-65-2P 866756-66-3P 866756-67-4P
866756-68-5P 866756-69-6P 866756-70-9P 866756-71-0P

866756-72-1P 866756-73-2P 866756-74-3P 866756-75-4P
866756-76-5P 866756-77-6P 866756-78-7P 866756-79-8P
866756-80-1P 866756-81-2P 866756-82-3P 866756-83-4P
866756-84-5P 866756-85-6P 866756-86-7P 866756-87-8P
866756-88-9P 866756-89-0P 866756-91-4P 866756-92-5P
866756-93-6P 866756-94-7P 866756-95-8P 866756-96-9P
866756-97-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of thiazole **tyrosine kinase** inhibitors)

IT 62-53-3, Aniline, reactions 99-61-6, 3-Nitrobenzaldehyde 100-46-9, Benzylamine, reactions 103-85-5 108-69-0, 3,5-Dimethylaniline 3034-52-4, 2-Chlorothiazole 10272-07-8, 3,5-Dimethoxyaniline 13889-98-0, 1-Acetylpiperazine 14371-25-6 51640-36-9, 2-Chlorothiazole-5-carbonitrile 62124-43-0, 2-Chloro-5-phenyl-1,3-oxazole 329794-40-3, 2-Chloro-5-phenyl-1,3-thiazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of thiazole **tyrosine kinase** inhibitors)

IT 133972-63-1P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of thiazole **tyrosine kinase** inhibitors)

L17 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:902904 HCAPLUS
DOCUMENT NUMBER: 141:388319
TITLE: Potent N-(1,3-Thiazol-2-yl)pyridin-2-amine Vascular Endothelial Growth Factor Receptor **Tyrosine Kinase** Inhibitors with Excellent Pharmacokinetics and Low Affinity for the hERG Ion Channel
AUTHOR(S): **Bilodeau, Mark T.**; Balitza, Adrienne E.; Koester, Timothy J.; Manley, Peter J.; Rodman, Leonard D.; Buser-Doepner, Carolyn; Coll, Kathleen E.; Fernandes, Christine; Gibbs, Jackson B.; Heimbrook, David C.; Huckle, William R.; Kohl, Nancy; Lynch, Joseph J.; Mao, Xianzhi; McFall, Rosemary C.; McLoughlin, Debra; Miller-Stein, Cynthia M.; Rickert, Keith W.;

Sepp-Lorenzino, Laura; Shipman, Jennifer M.; Subramanian, Raju; Thomas, Kenneth A.; Wong, Bradley K.; Yu, Sean; Hartman, George D.

CORPORATE SOURCE: Departments of Medicinal Chemistry, Cancer Research, Drug Metabolism and Pharmacology, Merck Research Laboratories, West Point, PA, 19486, USA

SOURCE: Journal of Medicinal Chemistry (2004), 47(25), 6363-6372
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:388319

AB A series of N-(1,3-thiazol-2-yl)pyridin-2-amine KDR kinase inhibitors have been developed that possess optimal properties. Compds. have been discovered that exhibit excellent in vivo potency. The particular challenges of overcoming hERG binding activity and QTc increases in vivo in addn. to achieving good pharmacokinetics have been accomplished by discovering a unique class of amine substituents. These compds. have a favorable kinase selectivity profile that can be accentuated with appropriate substitution.

CC 1-6 (Pharmacology)
Section cross-reference(s): 28

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

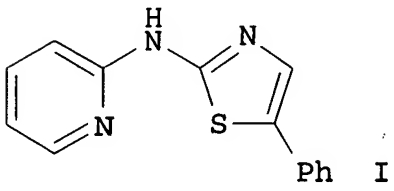
ACCESSION NUMBER: 2004:362591 HCAPLUS
DOCUMENT NUMBER: 141:106407
TITLE: The discovery of N-(1,3-thiazol-2-yl)pyridin-2-amines as potent inhibitors of KDR kinase

AUTHOR(S): **Bilodeau, Mark T.**; Rodman, Leonard D.; McGaughey, Georgia B.; Coll, Kathleen E.; Koester, Timothy J.; Hoffman, William F.; Hungate, Randall W.; Kendall, Richard L.; McFall, Rosemary C.; Rickert, Keith W.; Rutledge, Ruth Z.; Thomas, Kenneth A.

CORPORATE SOURCE: Departments of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(11), 2941-2945
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:106407
GI



I

AB An azo-dye lead was modified to a N-(1,3-thiazol-2-yl)pyridin-2-amine series of KDR kinase inhibitors through the use of rapid analog libraries. The two lead compds. were N-butyl-N,3-dimethyl-4-[(5-nitro-2-thiazolyl)azo]benzenamine and N-(5-phenyl-2-thiazolyl)benzamide. This class has been found to be potent, selective, and of low mol. wt. Mol. modeling has postulated an interesting conformational preference and binding mode for these compds. in the active site of the enzyme. A binding mode was proposed for the lead compd. N-(5-phenyl-2-thiazolyl)-2-pyridinamine (I) in the KDR kinase active site.

CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7

IT 150027-15-9, Kinase (phosphorylating), fibroblast growth factor type 1 receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FGFR-1 **tyrosine kinase** inhibitors; prepn. of N-(thiazolyl)pyridinamines, and analogs and study of their activity as KDR kinase inhibitors and structure-activity relationship)

IT 150316-06-6, Kinase (phosphorylating), fibroblast growth factor type 2 receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FGFR-2 **tyrosine kinase** inhibitors; prepn. of N-(thiazolyl)pyridinamines, and analogs and study of their activity as KDR kinase inhibitors and structure-activity relationship)

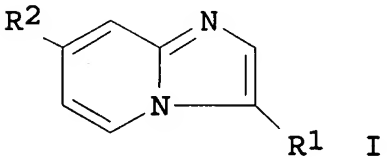
IT 150977-45-0, Gene KDR **tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(KDR **kinase** inhibitors; prepn. of N-

(thiazolyl)pyridinamines, and analogs and study of their activity as KDR kinase inhibitors and structure-activity relationship)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:892545 HCAPLUS
DOCUMENT NUMBER: 139:364935
TITLE: Preparation of imidazopyridines as **tyrosine kinase** inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Fraley, Mark E.; Wu, Zhicai
PATENT ASSIGNEE(S): Merck & Co., Inc, USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003092595	A2	20031113	WO 2003-US13353	20030428
WO 2003092595	A3	20040603		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2483084	AA	20031113	CA 2003-2483084	20030428
EP 1503757	A2	20050209	EP 2003-731058	200304

28
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
US 2005176753 A1 20050811 US 2003-512927 200304 28
JP 2005530745 T2 20051013 JP 2004-500780 200304 28
PRIORITY APPLN. INFO.: US 2002-377502P P 200205 02
WO 2003-US13353 W 200304 28
OTHER SOURCE(S): MARPAT 139:364935
GI



I

AB Imidazopyridines I [R1 = alkenyl, alkynyl, (un)substituted aryl, cycloalkyl, heteroaryl; R2 = (un)substituted aryl, cycloalkyl, heteroaryl] were prepd. for use as regulators of **tyrosine kinase** signal transduction in treatment of diseases, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases (no data). Thus, 4-iodopicolinic acid was converted to 2-tert.-butoxycarbonylamino-4-iodopyridine which was coupled with PhB(OH)2, deblocked, cyclized with BrCH2CHO, iodinated and coupled again with PhB(OH)2 to give I [R1, R2 = Ph].

IC ICM A61K
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
ST imidazopyridine prepn **tyrosine kinase** inhibitor
IT Eye, disease

(diabetic retinopathy; prepn. of imidazopyridines as **tyrosine kinase** inhibitors)

IT Eye, disease
(macula, degeneration; prepn. of imidazopyridines as **tyrosine kinase** inhibitors)

IT Angiogenesis
Angiogenesis inhibitors
Anti-inflammatory agents
Antitumor agents
Atherosclerosis
Human
Inflammation
Neoplasm
(prepn. of imidazopyridines as **tyrosine kinase** inhibitors)

IT 80449-02-1, **Tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of imidazopyridines as **tyrosine kinase** inhibitors)

IT 98-80-6, Phenylboronic acid 288-47-1, Thiazole 553-26-4, 4,4'-Bipyridine 1458-63-5, 1-(3-Chloropropyl)piperidine 16927-13-2, α-Bromophenylacetaldehyde 17157-48-1, Bromoacetaldehyde 55276-43-2, 1-Methanesulfonylpiperazine 87199-17-5, 4-Formylphenylboronic acid 90203-05-7, 3-Dimethylaminomethylpiperidine 405939-79-9, 4-Iodo-2-pyridinecarboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of imidazopyridines as **tyrosine kinase** inhibitors)

IT 39182-30-4P, 4,4'-Bipyridine 1-oxide 52311-42-9P, [4,4'-Bipyridin]-2-amine 53344-73-3P, 2-Chloro-4,4'-bipyridine 60781-83-1P 85102-27-8P, 7-Phenylimidazo[1,2-a]pyridine 201810-33-5P 405939-28-8P, 2-tert.-Butoxycarbonylamino-4-iodopyridine 453510-85-5P, 3-Bromo-7-phenylimidazo[1,2-a]pyridine 622402-25-9P 622402-26-0P, 3-Iodo-7-phenylimidazo[1,2-a]pyridine 622402-34-0P 622402-35-1P 622402-36-2P 622402-37-3P 622402-46-4P 622402-47-5P 622402-48-6P 622402-56-6P, 7-Phenylimidazo[1,2-a]pyridine-3-carboxaldehyde
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of imidazopyridines as **tyrosine kinase** inhibitors)

IT 622402-53-3P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or

reagent); USES (Uses)
(prepn. of imidazopyridines as **tyrosine kinase** inhibitors)

IT 622402-27-1P, 3,7-Diphenylimidazo[1,2-a]pyridine 622402-28-2P
622402-29-3P 622402-30-6P 622402-31-7P 622402-32-8P
622402-33-9P 622402-38-4P 622402-39-5P 622402-40-8P
622402-41-9P 622402-42-0P 622402-43-1P 622402-44-2P
622402-45-3P 622402-49-7P 622402-50-0P 622402-51-1P
622402-52-2P 622402-54-4P 622402-55-5P 622402-57-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of imidazopyridines as **tyrosine kinase** inhibitors)

L17 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:634666 HCAPLUS

TITLE: Development of 3-methylpyridin-2-yl-aminothiazole inhibitors of the VEGF receptor (KDR)

AUTHOR(S): Balitza, Adrienne E.; **Bilodeau, Mark T.**; Rodman, Leonard D.; Manley, Peter J.; Hartman, George D.; Coll, Kathleen E.; McFall, Rosemary C.; Rickert, Keith W.; Shipman, Jennifer M.; Shi, Bin; Sepp-Lorenzino, Laura; Buser-Doepner, Carolyn; Mao, Xianzhi; Thomas, Kenneth A.; Miller-Stein, Cynthia; Wong, Bradley K.

CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA

SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-057. American Chemical Society: Washington, D. C.
CODEN: 69EKY9

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Angiogenesis, the growth of new blood vessels from the established vasculature, has been implicated in the progression of such diseases as diabetic retinopathy, rheumatoid arthritis, and cancer. The growth and metathesis of solid tumors relies on the up-regulation of vascular endothelial growth factor (VEGF). The VEGF receptor **tyrosine kinase** VEGFR-2 (KDR) is a mitogenic receptor selectively expressed on endothelial cells. We have designed and synthesized a series of 3-methylpyridin-2-yl-aminothiazoles, a new class of potent KDR inhibitors with excellent

pharmacokinetic properties. A particular compd. will be highlighted which is potent in both enzyme and cell based assays and also has an exceptional pharmacokinetic profile in three species. Addnl., the 3-Me pyridine substituent has been shown to provide enhanced levels of kinase selectivity. A rationale for this selectivity enhancement, based on mol. modeling, will be provided.

L17 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:5956 HCAPLUS
DOCUMENT NUMBER: 138:73254
TITLE: Preparation of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses
INVENTOR(S): **Bilodeau, Mark T.**; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

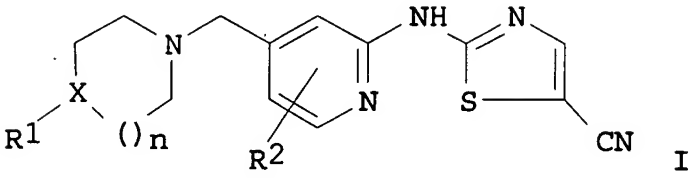
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000687	A1	20030103	WO 2002-US21110	20020618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2450562	AA	20030103	CA 2002-2450562	20020618
EP 1404672	A1	20040407	EP 2002-744810	20020618
EP 1404672	B1	20060118		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2004535437	T2	20041125	JP 2003-507090	20020618
AT 316088	E	20060215	AT 2002-744810	20020618
US 2003100567	A1	20030529	US 2002-174774	20020619
US 6875767	B2	20050405		
PRIORITY APPLN. INFO.:			US 2001-300245P P	20010622
			WO 2002-US21110 W	20020618

OTHER SOURCE(S): MARPAT 138:73254

GI



I

AB The present invention relates to thiazolylaminopyridines (shown as I; variables defined below; e.g. 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide) which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction, compns. which contain these compds., and methods of using them to treat **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. For I: n is 0 or 1; X is C-H or N, provided X is C-H if n = 1 and R1 is SO2-(C1-C6 alkyl) and provided

that X is C-H if R1 is NH(C:O)NR3H; R1 is SO2(C1-C6 alkyl), (C:O)NR3H, or NH(C:O)NR3H; R2 is H, OH, OC1-C6 alkyl, C1-C6 alkyl, or halo; and R3 is C1-C6 alkyl. Compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values = 0.01-5.0 μM. 4-[2-(5-Cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide, 2-[[4-[[4-(methylsulfonyl)piperidin-1-yl]methyl]pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile, and 4-[2-(5-cyanothiazol-2-ylamino)-3-methylpyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide show enhanced pharmacokinetic properties as compared to previously reported thiazolylaminopyridines in WO 01/17995 A1. Although the methods of prepn. are not claimed, 13 example prepns. are included.

IC ICM C07D417-12
ICS C07D417-14; A61K031-44; A61P035-00; A61P043-00; A61P027-02; A61P029-00; A61P019-02; A61P017-06; A61P017-00

CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7

ST thiazolylaminopyridine prepn **tyrosine kinase** inhibitor therapeutic use; pyridine thiazolylamino prepn **tyrosine kinase** inhibitor therapeutic use

IT Lung, neoplasm
(adenocarcinoma; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Antiarteriosclerotics
(antiatherosclerotics; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blockers; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT Mammary gland, neoplasm
(carcinoma; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Ischemia
(cerebral, tissue damage following; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Dermatitis
(contact; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Allergy
(delayed hypersensitivity; prepn. of thiazolylaminopyridines as

tyrosine kinase inhibitors with therapeutic uses)

IT Eye, disease
(diabetic retinopathy; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Neuroglia, neoplasm
(glioblastoma; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Lymphoma
(histiocytic; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Cytotoxic agents
Radiotherapy
(in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT Interleukin 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT Platelet-derived growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT Brain, disease
(ischemia, tissue damage following; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Eye, disease
(macula, degeneration, age-related; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Carcinoma
(mammary; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Lymph node, neoplasm
Neoplasm
(metastasis; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Signal transduction, biological
(modulators of **tyrosine kinase** signal

transduction; prepn. of thiazolylaminopyridines as)

IT Androgen receptors
Estrogen receptors
Retinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulators; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT Urogenital system
(neoplasm; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Angiogenesis
(neovascularization, retinal; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Bone, neoplasm
Sarcoma
(osteosarcoma; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Angiogenesis
Angiogenesis inhibitors
Anti-inflammatory agents
Antiarthritics
Antirheumatic agents
Antitumor agents
Atherosclerosis
Brain, neoplasm
Human
Inflammation
Larynx, neoplasm
Lung, neoplasm
Neoplasm
Osteoarthritis
Pancreas, neoplasm
Preeclampsia
Psoriasis
Rheumatoid arthritis
Rickets
Stomach, neoplasm
(prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Carcinoma
(pulmonary adenocarcinoma; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic

uses)

IT Carcinoma
(pulmonary small-cell; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Eye, disease
(retina, neovascularization; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Lung, neoplasm
(small-cell carcinoma; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT Troponins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(troponin-1; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αIIbβ3, antagonists; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MMP5, inhibitors; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT 479611-82-0P, 4-[[2-(5-Cyanothiazol-2-ylamino)pyridin-4-yl]methyl]piperazine-1-carboxylic acid methylamide 479611-88-6P, 2-[[4-[[4-(Methylsulfonyl)piperidin-1-yl]methyl]pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 479612-56-1P, 4-[2-(5-Cyanothiazol-2-ylamino)-3-methylpyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide trifluoroacetate
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT 479611-99-9P, N-[(3R)-1-[[2-[(5-Cyano-1,3-thiazol-2-yl)amino]pyridin-4-yl]methyl]pyrrolidin-3-yl]-N'-methylurea 479612-00-5P, N-[(3R)-1-[[2-[(5-Cyano-1,3-thiazol-2-yl)amino]pyridin-4-yl]methyl]pyrrolidin-3-yl]-N'-methylurea trifluoroacetate 479612-14-1P, 2-[[4-[[((3S)-5-Oxopyrrolidin-3-yl)amino]methyl]pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 479612-15-2P, 2-[[4-[[((3S)-5-Oxopyrrolidin-3-yl)amino]methyl]pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile trifluoroacetate 479612-28-7P, 4-[2-(5-Cyanothiazol-2-ylamino)-5-methylpyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide 479612-29-8P, 4-[[2-(5-Cyanothiazol-2-ylamino)-5-methylpyridin-4-yl]methyl]piperazine-1-carboxylic acid methylamide trifluoroacetate 479612-55-0P, 4-[2-(5-Cyanothiazol-2-ylamino)-3-methylpyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide 479612-74-3P, 4-[[2-Chloro-6-[(5-cyano-1,3-thiazol-2-yl)amino]pyridin-4-yl]methyl]-N-methylpiperazine-1-carboxamide 479612-92-5P, 4-[[2-[(5-Cyano-1,3-thiazol-2-yl)amino]-6-ethylpyridin-4-yl]methyl]-N-methylpiperazine-1-carboxamide 479613-12-2P, 2-[[4-[(4-Acetylpiperazin-1-yl)methyl]-6-methylpyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 479613-13-3P, 2-[[4-[(4-Acetylpiperazin-1-yl)methyl]-6-methylpyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile trifluoroacetate
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT 350496-88-7, Protein prenyltransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT 50-35-1, Thalidomide 10540-29-1, Tamoxifen 33069-62-4, Paclitaxel 84449-90-1, Raloxifene 86090-08-6, Angiostatin 99519-84-3 117048-59-6, Combretastatin A-4 132746-81-7 140207-93-8 144494-65-5, Tirofiban 148717-90-2, Squalamine 180288-69-1, Trastuzumab
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT 127464-60-2, Vascular endothelial growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of VEGF-stimulated mitogenesis of human vascular endothelial cells; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic

uses)

IT 9028-35-7, HMG-CoA reductase 9068-38-6, Reverse transcriptase 39391-18-9, Cyclooxygenase 62031-54-3, Fibroblast growth factor 62229-50-9, Epidermal growth factor 131384-38-8, Protein prenyltransferase 144114-21-6, HIV protease
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT 329900-75-6, COX-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (inhibitors; in combination with thiazolylaminopyridine **tyrosine kinase** inhibitors for various therapies)

IT 80449-02-1, **Tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT 4248-19-5, tert-Butyl carbamate 5327-32-2, N-(4-Methylpyridin-2-yl)acetamide 6313-54-8, 2-Chloroisonicotinic acid 13889-98-0, N-Acetylpiperazine 25462-85-5, 2-Chloro-6-methylisonicotinic acid 42521-08-4, 2,6-Dichloroisonicotinoyl chloride 51640-52-9, 2-Aminothiazole-5-carbonitrile 57260-71-6 58997-11-8, 3-Methylisonicotinic acid ethyl ester 109384-19-2, tert-Butyl 4-hydroxypiperidine-1-carboxylate 160806-40-6, (4S)-4-Aminopyrrolidin-2-one 479612-03-8, tert-Butyl (3R)-3-[(trifluoroacetyl)amino]pyrrolidine-1-carboxylate
RL: RCT (Reactant); RACT (Reactant or reagent) (prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)

IT 6937-03-7P, 2-Aminoisonicotinic acid methyl ester 51640-36-9P, 2-Chlorothiazole-5-carbonitrile 54221-95-3P, 2-Acetylaminoisonicotinic acid 101990-69-6P, (2,6-Dichloropyridin-4-yl)methanol 105250-17-7P, (2-Aminopyridin-4-yl)methanol 131418-11-6P, 2-Chloro-N-methylisonicotinamide 141699-59-4P, tert-Butyl 4-[(methylsulfonyl)oxy]piperidine-1-carboxylate 147081-49-0P, tert-Butyl (3R)-3-aminopyrrolidine-1-carboxylate 152815-18-4P, (2-Chloro-6-methylpyridin-4-yl)methanol 189205-49-0P, tert-Butyl 4-(methylsulfonyl)piperidine-1-carboxylate 208245-69-6P, tert-Butyl 4-(methylthio)piperidine-1-carboxylate 221095-71-2P, 4-(tert-Butyldimethylsilanyloxymethyl)-2,6-dichloropyridine 301666-87-5P, 3-Methyl-1-oxoisonicotinic acid ethyl ester 329794-09-4P, 4-(tert-Butyldimethylsilanyloxymethyl)pyridin-2-ylamine 329794-13-0P, 2-[4-(tert-

Butyldimethylsilanyloxymethyl)pyridin-2-ylamino]thiazole-5-carbonitrile 329794-14-1P, 2-(4-Hydroxymethylpyridin-2-ylamino)thiazole-5-carbonitrile 329794-15-2P, 2-[[4-(Chloromethyl)pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 329794-45-8P, (2-Chloro-3-methylpyridin-4-yl)methanol 479611-85-3P, 1-[(Methylamino)carbonyl]piperazin-4-ium chloride 479611-96-6P, 4-(Methylsulfonyl)piperidine hydrochloride 479612-08-3P, tert-Butyl (3R)-3-[[(methylamino)carbonyl]amino]pyrrolidine-1-carboxylate 479612-11-8P, N-Methyl-N'-((3R)-pyrrolidin-3-yl)urea monohydrochloride 479612-25-4P, 2-Chloro-3,N-dimethylisonicotinamide 479612-36-7P, (2-Chloro-5-methylpyridin-4-yl)methanol 479612-40-3P, 4-(tert-Butyldimethylsilanyloxymethyl)-2-chloro-5-methylpyridine 479612-42-5P, 4-(tert-Butyldimethylsilanyloxymethyl)-5-methylpyridin-2-ylamine 479612-44-7P, 2-[4-(tert-Butyldimethylsilanyloxymethyl)-5-methylpyridin-2-ylamino]thiazole-5-carbonitrile 479612-47-0P, 2-(4-Hydroxymethyl-5-methylpyridin-2-ylamino)thiazole-5-carbonitrile 479612-50-5P, 2-(4-Chloromethyl-5-methylpyridin-2-ylamino)thiazole-5-carbonitrile 479612-59-4P, 4-(tert-Butyldimethylsilanyloxymethyl)-2-chloro-3-methylpyridine 479612-62-9P, 4-(tert-Butyldimethylsilanyloxymethyl)-3-methylpyridin-2-ylamine 479612-65-2P, 2-[4-(tert-Butyldimethylsilanyloxymethyl)-3-methylpyridin-2-ylamino]thiazole-5-carbonitrile 479612-68-5P, 2-(4-Hydroxymethyl-3-methylpyridin-2-ylamino)thiazole-5-carbonitrile 479612-71-0P, 2-(4-Chloromethyl-3-methylpyridin-2-ylamino)thiazole-5-carbonitrile 479612-81-2P, tert-Butyl 4-[[(tert-butyldimethylsilyl)oxy]methyl]-6-chloropyridin-2-ylcarbamate 479612-84-5P, 4-(tert-Butyldimethylsilanyloxymethyl)-6-chloropyridin-2-ylamine 479612-86-7P, 2-[4-(tert-Butyldimethylsilanyloxymethyl)-6-chloropyridin-2-ylamino]thiazole-5-carbonitrile 479612-87-8P, 2-[[6-Chloro-4-(hydroxymethyl)pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 479612-90-3P, 2-[[6-Chloro-4-(chloromethyl)pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 479612-95-8P, 4-[[(tert-Butyldimethylsilyl)oxy]methyl]-6-ethylpyridin-2-amine 479613-00-8P, tert-Butyl 4-[[(tert-butyldimethylsilyl)oxy]methyl]-6-ethylpyridin-2-ylcarbamate 479613-03-1P, 2-[[4-[[(tert-Butyldimethylsilyl)oxy]methyl]-6-ethylpyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 479613-06-4P, 2-[[6-Ethyl-4-(hydroxymethyl)pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 479613-09-7P, 2-[[4-(Chloromethyl)-6-ethylpyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile 479613-16-6P, 2-Chloro-6-methylpyridine-4-carboxaldehyde 479613-21-3P, tert-Butyl 4-[(4-acetylpiperazin-1-yl)methyl]-6-methylpyridin-2-ylcarbamate 479613-24-6P, tert-Butyl 4-formyl-6-methylpyridin-2-ylcarbamate 479613-27-9P, 1-Acetyl-4-[(2-amino-6-methylpyridin-4-yl)methyl]piperazin-4-ium

chloride
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of thiazolylaminopyridines as **tyrosine kinase** inhibitors with therapeutic uses)
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:790223 HCAPLUS
DOCUMENT NUMBER: 137:310915
TITLE: Preparation of benzimidazole and imidazopyridine derivatives as angiogenesis inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Hungate, Randall W.; Cunningham, April M.; Koester, Timothy J.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 143,881, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6465484	B1	20021015	US 2001-786004	20010228
WO 2000012089	A1	20000309	WO 1999-US5297	19990311

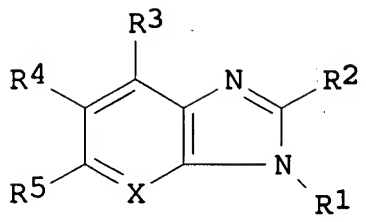
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1997-60151P P 19970926

US 1998-143881 B2
199808
31

WO 1999-US5297 W
199903
11

OTHER SOURCE(S): MARPAT 137:310915
GI



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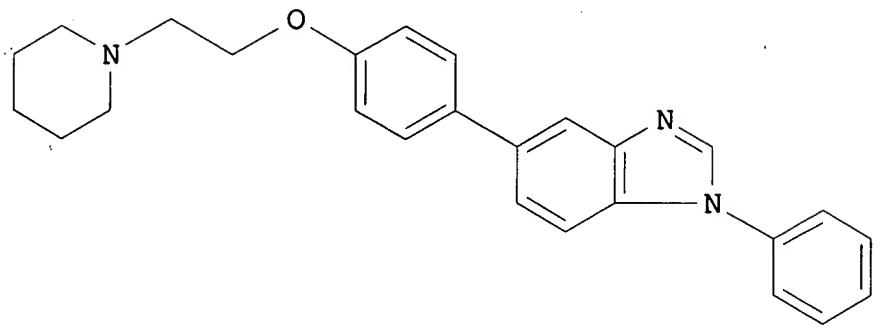


II

AB Title compds. I [X = N; R1 = aryl, heterocyclyl, heteroaryl; R2-3, R5 = H, alkyl; R4 = H, alkyl] were prepd. For instance, 1-Bromo-4-fluoro-3-nitrobenzene was reacted with aniline (NMP, i-Pr2NEt, 120°, 14 h), the product coupled to 4-methoxyboronic acid (dioxane/water, Na2CO3, [PPh3]4Pd, 80°, 14 h) and the biaryl reduced (EtOH/HOAc, Pd/C-H2, 2 h) and the

resulting intermediate treated with (MeO)3CH at 120° for 30 min to afford 1-phenyl-5-(4-methoxyphenyl)benzimidazole. This was demethylated (CH3CN/CH2Cl2, AlCl3, NaI, reflux, 44 h) and the resulting phenol reacted with 1-(2-chloroethyl)piperidine hydrochloride (DMF, Cs2CO3, 50°) to give II. Compds. of the invention inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 150-650 nM. I are useful for the treatment of **tyrosine kinase** -dependent diseases/conditions such as angiogenenesis, cancer, atherosclerosis, diabetic retinopathy or autoimmune diseases.

IC ICM A61K031-437
ICS A61K031-506; A61K031-4184; C07D401-12; C07D409-14; C07D417-14
INCL 514303000
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
ST angiogenesis inhibitor **tyrosine kinase** cancer VEGF prepn
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:467028 HCAPLUS
DOCUMENT NUMBER: 137:362282
TITLE: Kinase insert domain-containing receptor kinase inhibitors as anti-angiogenic agents
AUTHOR(S): **Bilodeau, Mark T.**; Fraley, Mark E.; Hartman, George D.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Expert Opinion on Investigational Drugs (2002), 11(6), 737-745
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. A variety of data accumulated during the past 10 yr indicates that vascular endothelial growth factor-mediated angiogenesis is a key process in the growth of solid tumors. Efficacious and specific modulation of that signalling event through the inhibition of the cognate **tyrosine kinase** **kinase** insert domain-contg. receptor (Flk-1) has been reported. A variety of small mol. kinase-domain-contg. receptor kinase inhibitors, including SU-5416, SU-6668, PTK-787, midostaurin,

ZD4190 and ZD6474, have progressed to the clin. testing stage and this has allowed the direct and crit. inspection of preclin. and clin. behavior. The variety of potency, kinase selectivity and pharmacokinetic profiles offered by this group of compds. is providing important guidance for the efficacious use of these agents today and the design of second and third generation compds. for the future.

CC 1-0 (Pharmacology)

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:449449 HCAPLUS

DOCUMENT NUMBER: 137:33318

TITLE: Preparation of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors.

INVENTOR(S): **Bilodeau, Mark T.**; Hartman, George D.; Hoffman, Jacob M., Jr.; Lumma, William C., Jr.; Manley, Peter J.; Rodman, Leonard; Sisko, John T.; Smith, Anthony M.; Tucker, Thomas J.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 169 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002045652	A2	20020613	WO 2001-US44573	200111 30
WO 2002045652	A3	20020822		

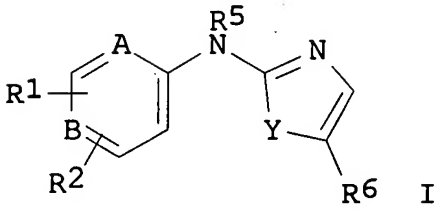
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,

	SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2002137755		A1	20020926	US 2001-990473 200111 21
CA 2429728		AA	20020613	CA 2001-2429728 200111 30
AU 2002032441		A5	20020618	AU 2002-32441 200111 30
EP 1341540		A2	20030910	EP 2001-991965 200111 30
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2004524282		T2	20040812	JP 2002-547438 200111 30
US 2004063720		A1	20040401	US 2003-677687 200310 02
PRIORITY APPLN. INFO.:				US 2000-251006P P 200012 04
				US 2001-990473 A1 200111 21
				WO 2001-US44573 W 200111 30

OTHER SOURCE(S): MARPAT 137:33318

GI



I

AB Title compds. [I; A, B = N, NO; Y = O, S, NR4; R1, R2 = H, perfluoroalkoxy, OH, cyano, halo, (substituted) alkyl(oxy)(carbonyl), aryl(oxy)(carbonyl), heterocyclyl, etc.; R4 = H, aryl, alkyl; R5 = H, SO2Rc, CORc, Rc, CO2Rc; R6 = aryl, cyano, halo, (substituted) alkyl, alkenyl, alkynyl, heterocyclyl, aminocarbonyl; Rc = alkyl, aryl, heterocyclyl], were prepd. for treating angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammation, etc. Thus, 4-aminopyrimidine was stirred with NaH in THF; 2-bromo-5-phenylthiazole was added and the mixt. was refluxed overnight to give 5-phenylthiazol-2-yl pyrimidin-4-yl amine. I inhibited vascular endothelial growth factor-stimulated mitogenesis of human vascular endothelial cells with IC50 = 0.01-5.0 nM.

IC ICM A61K

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST piperazinylpyrimidinylaminothiazole prepn **tyrosine kinase** inhibitor; pyrimidinylaminothiazole prepn **tyrosine kinase** inhibitor; thiazole pyrimidinylamino prepn **tyrosine kinase** inhibitor; anticancer pyrimidinylaminothiazole prepn; vegf inhibitor pyrimidinylaminothiazole prepn

IT Leukemia
(acute myeloid, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Meningitis
(bacterial, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Interleukin 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Intestine, neoplasm
(colorectal, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Dermatitis
(contact, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Allergy
(delayed hypersensitivity, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Eye, disease

(diabetic retinopathy, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Uterus, disease
(endometriosis, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Neuroglia, neoplasm
(glioblastoma, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Eye, disease
(macula, degeneration, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Androgen receptors
Estrogen receptors
Retinoid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulators; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Bone, neoplasm
Sarcoma
(osteosarcoma, treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Angiogenesis inhibitors
Anti-inflammatory agents
Antiarthritics
Antitumor agents
Cytotoxic agents
Human
(prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Eye
(retina, treatment of retinal vascularization; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Lymphatic system
(treatment of cancer; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Angiogenesis
Brain, neoplasm
Eye, disease
Inflammation
Larynx, neoplasm
Leukemia
Lymphoma

Mammary gland, neoplasm
Osteoarthritis
Pancreas, neoplasm
Prostate gland, neoplasm
Psoriasis
Rheumatoid arthritis
Rickets
Stomach, neoplasm
(treatment; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α, coadministration; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, agonists; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT 50-35-1, Thalidomide 10540-29-1, Tamoxifen 33069-62-4, Paclitaxel 84449-90-1, Raloxifene 86090-08-6, Angiostatin 117048-59-6, Combretastatin A-4 129497-78-5, Verteporfin 132746-81-7, 6-O-(N-Chloroacetylcarbamoyl)fumagillol 140207-93-8 144494-65-5, Tirofiban 148717-90-2, Squalamine 180288-69-1, Trastuzumab 391966-14-6, Troponin I (human)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT 9028-35-7, HMG-CoA reductase 9068-38-6, Reverse transcriptase 80449-02-1, **Tyrosine kinase** 144114-21-6, HIV protease 340830-03-7, Receptor **tyrosine kinase** 350496-88-7, Protein prenyltransferase 386705-49-3, VEGF receptor **tyrosine kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT 436850-69-0P, N-(5-Phenyl-thiazol-2-yl)-N-(pyrimidin-4-yl)amine 436850-71-4P 436850-73-6P 436850-74-7P, 2-[(2-Aminopyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile 436850-75-8P, 2-[(6-Aminopyrimidin-4-yl)amino]-1,3-thiazole-5-carbonitrile 436850-76-9P 436850-77-0P 436850-78-1P 436850-79-2P 436850-80-5P 436850-81-6P 436850-82-7P 436850-83-8P 436850-84-9P 436850-85-0P 436850-87-2P 436850-89-4P 436850-91-8P 436850-92-9P 436850-94-1P 436850-96-3P 436850-98-5P 436851-00-2P 436851-01-3P 436851-02-4P 436851-03-5P 436851-04-6P 436851-05-7P 436851-06-8P

436851-07-9P 436851-08-0P 436851-09-1P 436851-10-4P
436851-12-6P 436851-14-8P 436851-15-9P 436851-17-1P
436851-19-3P 436851-21-7P 436851-23-9P 436851-24-0P
436851-26-2P 436851-28-4P 436851-30-8P 436851-32-0P
436851-34-2P 436851-36-4P 436851-38-6P 436851-40-0P
436851-41-1P 436851-42-2P 436851-43-3P 436851-44-4P
436851-45-5P 436851-46-6P 436851-47-7P 436851-48-8P
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436851-57-9P 436851-58-0P 436851-59-1P 436851-60-4P
436851-61-5P 436851-62-6P 436851-63-7P 436851-64-8P
436851-65-9P 436851-66-0P 436851-67-1P 436851-68-2P
436851-69-3P 436851-70-6P 436852-19-6P, 2-(Pyrimidin-4-ylamino)thiazole-5-carbonitrile 436852-24-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT 75-31-0, Isopropylamine, reactions 75-64-9, tert-Butylamine, reactions 96-50-4, 2-Aminothiazole 97-97-2, 2-Chloro-1,1-dimethoxyethane 110-91-8, Morpholine, reactions 111-95-5, 2-Methoxy-N-(2-methoxyethyl)ethanamine 156-81-0, 2,4-Diaminopyrimidine 461-98-3, 4-Amino-2,6-dimethylpyrimidine 591-54-8, 4-Aminopyrimidine 598-21-0, Bromoacetyl bromide 624-83-9, Methyl isocyanate 696-45-7 1193-21-1, 4,6-Dichloropyrimidine 1692-15-5, 4-Pyridineboronic acid 1749-68-4, 2-Methyl-4-chloro-6-aminopyrimidine 1913-09-3 2516-34-9, Cyclobutylamine 2516-47-4, Cyclopropylmethaneamine 3289-47-2 3289-50-7 3473-63-0, Formamidine acetate 3699-54-5, 1-(2-Hydroxyethyl)imidazolidin-2-one 4892-89-1, 4-(2-(Piperazin-1-yl)ethyl)morpholine 5292-43-3, tert-Butyl bromoacetate 7461-50-9, 2-Chloropyrimidin-4-amine 10132-07-7, 2,4-Dichloro-6-aminopyrimidine 13484-40-7, 1-(2-Methoxyethyl)piperazine 13889-98-0, 1-Acetylpiperazine 14394-56-0 15953-83-0, 3-Chlorothietane 1,1-dioxide 22763-69-5, 1-(2-(Pyrrolidin-1-yl)ethyl)piperazine 31166-44-6, Benzyl piperazine-1-carboxylate 34433-86-8, 3-Bromopiperidin-2-one 39093-93-1, Thiomorpholine dioxide 39890-42-1, N-Isopropyl-2-(piperazin-1-yl)acetamide 39890-45-4, 1-(2-Oxo-2-(pyrrolidin-1-yl)ethyl)piperazine 40299-87-4, 4-(Bromoacetyl)morpholine 41051-15-4, Methyl 4-methoxyacetoacetate 51640-36-9, 2-Chlorothiazole-5-nitrile 51642-03-6 57260-71-6 69206-89-9 73874-95-0 75726-96-4 77600-79-4, 2-Bromo-N-cyclopropylacetamide 77709-02-5 88675-24-5,

3-Aminotetrahydrofuran 96225-80-8 96225-96-6 99724-19-3
101385-93-7, tert-Butyl 3-oxopyrrolidine-1-carboxylate
112275-50-0, tert-Butyl 1,4-diazepane-1-carboxylate 113451-59-5
115943-91-4 126937-41-5 133311-51-0, 2-Bromo-5-phenylthiazole
138022-02-3 157688-46-5 184637-48-7, tert-Butyl
3-aminopiperidine-1-carboxylate 329794-40-3, 2-Chloro-5-
phenylthiazole 344779-09-5 436852-01-6 436852-18-5,
4-(3-(Piperazin-1-yl)propyl)morpholine 436852-21-0 436852-22-1
436852-23-2 436852-25-4 436852-26-5 436852-27-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

IT 2387-20-4P 3122-78-9P, 6-(Methoxymethyl)pyrimidin-4-ol
3122-84-7P, 4-Chloro-6-(methoxymethyl)pyrimidine 5305-59-9P,
6-Chloropyrimidin-4-amine 57005-70-6P 104087-61-8P
111009-94-0P 112257-12-2P 436851-71-7P 436851-72-8P
436851-73-9P 436851-74-0P 436851-75-1P 436851-76-2P
436851-77-3P 436851-78-4P 436851-79-5P 436851-80-8P
436851-81-9P 436851-82-0P 436851-83-1P 436851-84-2P
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436852-03-8P 436852-04-9P 436852-05-0P 436852-06-1P
436852-07-2P 436852-08-3P 436852-09-4P 436852-10-7P
436852-11-8P 436852-12-9P 436852-13-0P 436852-14-1P
436852-15-2P 436852-16-3P 436852-17-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrimidinylaminothiazoles as **tyrosine kinase** inhibitors)

L17 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:190380 HCAPLUS
TITLE: Development and in vivo evaluation of novel inhibitors of the VEGF receptor **tyrosine kinase** KDR (VEGFR-2)
AUTHOR(S): **Bilodeau, Mark T.**; Coll, Kathleen E.; Cunningham, April M.; Hartman, George D.; Huckle, William R.; Hungate, Randall W.; Kendall, Richard L.; Koester, Timothy J.; Rodman, Leonard D.; McFall, Rosemary C.; Mao, Xianzhi; Rutledge, Ruth E.; Thomas, Kenneth A.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486,

USA
SOURCE: Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002 (2002), MEDI-261. American Chemical Society: Washington, D. C.
CODEN: 69CKQP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB VEGF induces vascular endothelial cell mitogenic signaling and angiogenesis through the receptor **tyrosine kinase** KDR (VEGFR-2). The inhibition of this process has been a leading target in the search for anti-angiogenic therapeutics. We have been engaged in developing inhibitors of KDR kinase enzyme activity and we will describe efforts in two independently discovered series of inhibitors, benzimidazoles and thiazolylpyridyl amines. We will outline the set of in vitro and in vivo assays that forms our paradigm for development candidate selection. The thiazolylpyridyl amine series of inhibitors evolved from several iterations of library synthesis from an initial screening lead. The resulting series has provided potent inhibitors contg. structural elements assocd. with high levels of kinase selectivity, good cell potency, and excellent pharmacokinetics. Key compds. have been evaluated for their in vivo inhibitory activity of KDR autophosphorylation in mouse lung, angiogenesis in matrigel and the growth of tumor xenografts.

L17 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:202047 HCAPLUS
TITLE: Design and synthesis of 1,5-diarylbenzimidazoles as inhibitors of the VEGF-receptor KDR
AUTHOR(S): **Bilodeau, Mark T.**; Coll, Kathleen E.; Cunningham, April M.; Huckle, William R.; Hungate, Randall W.; Kendall, Richard L.; Koester, Timothy J.; McFall, Rosemary C.; Mao, Xianzhi; Rutledge, Ruth E.; Thomas, Kenneth A.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Abstracts of Papers, 221st ACS National Meeting, San Diego, CA, United States, April 1-5, 2001 (2001) MEDI-147
CODEN: 69FZD4
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; Meeting Abstract
LANGUAGE: English

AB Vascular endothelial growth factor (VEGF) is a specific growth factor for endothelial cells and efforts to disrupt its action represent a leading area in the search for anti-angiogenic therapeutics. Small mol. inhibitors of KDR (VEGFR-2), the VEGF-receptor **tyrosine kinase** involved in mitogenic signaling, have been identified and a few are undergoing clin. study as promising new anti-angiogenic agents. We have designed and synthesized a series of 1,5-diarylbenzimidazoles as potent inhibitors of KDR. We have examd. structure-activity relationships around the benzimidazole ring and related heterocyclic rings and the details of the synthesis and activities of these compds. will be presented. In addn., the optimization of cell potency and phys. properties in the series and the identification of compds. possessing good pharmacokinetic profiles will be presented.

L17 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:185751 HCAPLUS
DOCUMENT NUMBER: 134:222709
TITLE: Preparation of N-(pyrid-2-yl)-2-thiazolamines as **tyrosine kinase** inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Hungate, Randall W.; Rodman, Leonard; Hartman, George D.; Manley, Peter J.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 177 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001017995	A1	20010315	WO 2000-US24432	200009 06

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,

BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2384101	AA	20010315	CA 2000-2384101	20000906
AU 2000073517	A5	20010410	AU 2000-73517	20000906
AU 779908	B2	20050217		
EP 1218376	A1	20020703	EP 2000-961583	20000906
EP 1218376	B1	20051109		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003509342	T2	20030311	JP 2001-522218	20000906
BR 2000013899	A	20030708	BR 2000-13899	20000906
EE 200200123	A	20030815	EE 2002-123	20000906
AT 309241	E	20051115	AT 2000-961583	20000906
US 2002147203	A1	20021010	US 2002-62351	20020201
US 6586424	B2	20030701		
US 2003064996	A1	20030403	US 2002-61817	20020201
US 6586423	B2	20030701		
BG 106465	A	20021229	BG 2002-106465	20020228
ZA 2002001898	A	20030307	ZA 2002-1898	20020307
NO 2002001166	A	20020425	NO 2002-1166	20020308
PRIORITY APPLN. INFO.:			US 1999-153348P P	19990909

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WO 2000-US24432 W 20000906

US 2000-658680 B1 20000908

OTHER SOURCE(S): MARPAT 134:222709

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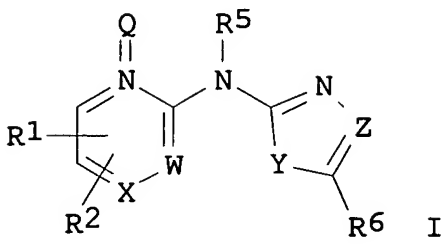

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AB The title compds. [I; XW = CC, NC, CN; Y = O, S, NR4; Z = N, CR4; Q = O, absent; R1, R2 = H, OH, CN, etc.; R5 = H, SO2Rc, CO2Rc, etc.; R6 = aryl, CN, cycloalkyl, etc.; Rc = alkyl, cycloalkyl, aryl, heterocyclyl] which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction, and therefore are useful in treating **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals, were prepd. Thus, refluxing 2-pyridylthiourea with (1-bromo-2,2-dimethoxyethyl)benzene in EtOH/HCl afforded the amine I [WX = CC; Y = S; Z = CH; Q = absent; R1, R2, R5 = H; R6 = Ph]. The compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 of 0.01-5.0 μM.

IC ICM C07D413-12
ICS C07D417-12; A61K031-4178; A61K031-4196; A61K031-422; A61K031-427; A61K031-433

CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST pyridylthiazolamine prepn **tyrosine kinase** VEGF inhibitor; thiazolamine pyridyl prepn **tyrosine**

kinase VEGF inhibitor; angiogenesis inhibitor
pyridylthiazolamine prepn; antitumor pyridylthiazolamine prepn

IT Angiogenesis
Antitumor agents
(prepn. of N-(pyrid-2-yl)-2-thiazolamines as **tyrosine kinase** inhibitors)

IT 60794-55-0P 329792-37-2P 329792-39-4P 329792-40-7P
329792-41-8P 329792-42-9P 329792-43-0P 329792-44-1P
329792-45-2P 329792-46-3P 329792-47-4P 329792-48-5P
329792-49-6P 329792-50-9P 329792-51-0P 329792-52-1P
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329792-69-0P 329792-70-3P 329792-71-4P 329792-72-5P
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329793-91-1P 329793-93-3P 329793-94-4P 329793-95-5P
329793-97-7P 329793-98-8P 329793-99-9P 329794-20-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-(pyrid-2-yl)-2-thiazolamines as **tyrosine kinase** inhibitors)

IT 127464-60-2, Vascular endothelial growth factor
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(prepn. of N-(pyrid-2-yl)-2-thiazolamines as **tyrosine kinase** inhibitors)

IT 107-19-7, Propargyl alcohol 110-89-4, Piperidine, reactions 504-29-0, 2-Aminopyridine 1072-97-5, 2-Amino-5-bromopyridine 1603-40-3, 2-Amino-3-methylpyridine 1824-81-3, 6-Methyl-2-pyridinamine 4543-96-8, N,N,N'-Trimethyl-1,3-propanediamine 5327-32-2 5623-95-0, 1-Piperazinecarboxamide 6313-54-8, 2-Chloroisonicotinic acid 13889-98-0, 1-Acetylpiperazine 14294-11-2, 2-Pyridylthiourea 14492-09-2 16419-60-6, o-Tolylboronic acid 17282-04-1, 2-Chloro-3-fluoropyridine 31437-20-4, 2-Pyrimidinylthiourea 36052-26-3, Methyl 6-aminopyridine-2-carboxylate 39093-93-1, Thiomorpholine-1,1-dioxide 41340-78-7, N,N-Dimethyl-1-piperazinecarboxamide 42521-10-8 51640-52-9 55276-43-2 88016-17-5 329794-40-3 329794-41-4 329794-42-5 329794-43-6 329794-44-7 329794-45-8 329794-46-9 329794-47-0 329794-48-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of N-(pyrid-2-yl)-2-thiazolamines as **tyrosine kinase** inhibitors)

IT 6937-03-7P 49600-34-2P 51640-36-9P 54221-95-3P 54670-78-9P 54670-80-3P 79651-64-2P 89226-77-7P 105250-17-7P 193001-91-1P 250263-39-9P 329794-00-5P 329794-01-6P 329794-02-7P 329794-03-8P 329794-04-9P 329794-05-0P 329794-06-1P 329794-07-2P 329794-08-3P 329794-09-4P 329794-10-7P 329794-11-8P 329794-12-9P 329794-13-0P 329794-14-1P 329794-15-2P 329794-16-3P 329794-17-4P 329794-18-5P 329794-21-0P 329794-22-1P 329794-23-2P 329794-24-3P 329794-25-4P 329794-26-5P 329794-27-6P 329794-28-7P 329794-29-8P 329794-30-1P 329794-31-2P 329794-32-3P 329794-33-4P 329794-34-5P 329794-35-6P 329794-36-7P 329794-37-8P 329794-38-9P 329794-39-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-(pyrid-2-yl)-2-thiazolamines as **tyrosine kinase** inhibitors)

IT 131418-11-6P

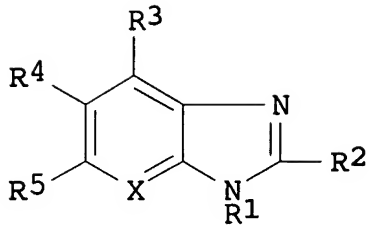
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of N-(pyrid-2-yl)-2-thiazolamines as **tyrosine kinase** inhibitors)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:891563 HCAPLUS
DOCUMENT NUMBER: 134:42130
TITLE: Benzimidazole derivatives as **tyrosine kinase** inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Cunningham, April M.; Hungate, Randall W.; Koester, Timothy J.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: U.S., 21 pp., Cont.-in-part of U.S. Ser. No. 143,881, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6162804	A	20001219	US 1999-266331		19990311
PRIORITY APPLN. INFO.:			US 1997-60151P	P	19970926
			US 1998-143881	B2	19980831

OTHER SOURCE(S): MARPAT 134:42130
GI



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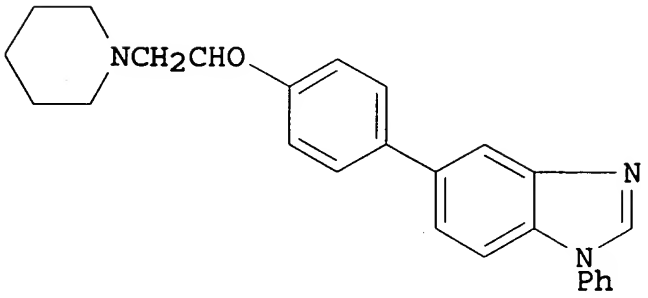


II

AB Benzimidazoles I [X = CH, N; R1 = (un)substituted Ph, thienyl, thiazolyl; R2, R3 = H, alkyl, aryl, cycloalkyl, OH, NO2, NH2, halo; R4 = (un)substituted Ph, pyridinyl, pyrimidinyl, etc.; R5 = H, alkyl, alkoxy, aryloxy, halo, NH2, NO2, etc.] were prepd. as **tyrosine kinase** inhibitors. Thus, II was prepd. in 6 steps starting from 4-bromo-1-fluoro-2-nitrobenzene and proceeding via 4'-methoxy-3-nitro-N-phenyl-4-biphenylamine. The products were inhibitors of vascular endothelial growth factor (VEGF) and inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values of 150-650 nM.

IC ICM A61K031-506
ICS A61K031-4184; A61K031-4545; C07D401-14; C07D403-14; C07D413-14

INCL 514234500

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST benzimidazole deriv prepn **tyrosine kinase** inhibitor; vascular endothelial growth factor inhibitor benzimidazole deriv

IT 221636-03-9P 221636-05-1P 221636-11-9P 260258-93-3P 260258-97-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(benzimidazole derivs. as **tyrosine kinase** inhibitors)

IT 2038-03-1P, 4-Morpholineethanamine 2622-60-8P 22358-63-0P
25660-38-2P 25699-94-9P 25699-95-0P 27578-60-5P,
1-Piperidineethanamine 221636-15-3P 221636-22-2P 221636-28-8P
221636-30-2P 221636-37-9P 221636-38-0P 221636-39-1P
221636-40-4P 260258-16-0P 260258-17-1P 260258-19-3P
260258-20-6P 260258-21-7P 260258-23-9P 260258-24-0P
260258-26-2P 260258-27-3P 260258-28-4P 260258-29-5P
260258-30-8P 260258-32-0P 260258-33-1P 260258-35-3P
260258-36-4P 260258-37-5P 260258-39-7P 260258-40-0P
260258-41-1P 260258-42-2P 260258-43-3P 260258-44-4P
260258-45-5P 260258-46-6P 260258-48-8P 260258-49-9P
260258-50-2P 260258-51-3P 260258-52-4P 260258-53-5P
260258-54-6P 260258-55-7P 260258-56-8P 260258-57-9P
260258-58-0P 260258-60-4P 260258-61-5P 260258-62-6P
260258-63-7P 260258-64-8P 260258-66-0P 260258-67-1P
260258-69-3P 260258-70-6P 260258-71-7P 260258-72-8P
260258-74-0P 260258-75-1P 260258-77-3P 260258-78-4P
260258-79-5P 260258-82-0P 260258-84-2P 260258-88-6P
260258-89-7P 260258-92-2P 260258-99-9P 312959-29-8P
312959-30-1P 312959-31-2P 312959-32-3P 312959-33-4P
312959-34-5P 312959-35-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(benzimidazole derivs. as **tyrosine kinase** inhibitors)

IT 80449-02-1, **Tyrosine kinase** 127464-60-2,
Vascular endothelial growth factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(benzimidazole derivs. as **tyrosine kinase** inhibitors)

IT 62-53-3, Aniline, reactions 364-73-8 766-11-0,
5-Bromo-2-fluoropyridine 1458-63-5, Piperidine,
1-(3-chloropropyl)- 2008-75-5, 1-(2-Chloroethyl)piperidine
hydrochloride 5720-07-0, 4-Methoxyphenylboronic acid 13472-79-2
15862-34-7 49844-90-8 73183-34-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(benzimidazole derivs. as **tyrosine kinase** inhibitors)

IT 16588-25-3P 77064-57-4P 221636-02-8P 221636-04-0P
221636-08-4P 221636-13-1P 221636-18-6P 221636-20-0P
260258-94-4P 260258-95-5P 260258-96-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(benzimidazole derivs. as **tyrosine kinase** inhibitors)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

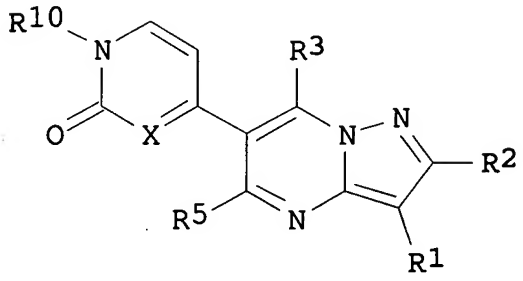
L17 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:646013 HCAPLUS
DOCUMENT NUMBER: 133:238017
TITLE: Preparation of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Fraley, Mark E.; Hungate, Randall W.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000053605	A1	20000914	WO 2000-US5903	20000308
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6245759	B1	20010612	US 2000-519780	20000307
CA 2366644	AA	20000914	CA 2000-2366644	20000308
EP 1161433	A1	20011212	EP 2000-914843	

20000308
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 2002539126 T2 20021119 JP 2000-604041
20000308
US 6544988 B1 20030408 US 2001-914985
20010906
PRIORITY APPLN. INFO.: US 1999-123902P P
19990311
WO 2000-US5903 W
20000308

OTHER SOURCE(S): MARPAT 133:238017

GI



I

AB The title compds. [I; X = CH, N; R1, R3 = H, alkyl, alkenyl, etc.; R2 = H, alkyl, aryl, etc.; R5 = H, alkyl, OH, etc.; R10 = H, alkyl, NR7R8, etc.; R7, R8 = H, alkyl, aryl, etc.; NR7R8 = (un)satd. (un)substituted 5-10 membered heterocyclyl contg., in addn. to the N atom, one to two addnl. heteroatoms selected from N, O, and S] which inhibit, regulate and/or modulate **tyrosine kinase** signal transduction, and therefore are useful in treating **tyrosine kinase**-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals, were prepd. E.g., a multi-step synthesis of I [X = CH; R1 = Ph; R2, R3, R5 = H; R10 =

3-(piperidin-1-yl)propyl] was given. Compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 of 0.01-5.0 μM.

IC ICM C07D487-04
ICS A61K031-519

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST pyrazolopyrimidine prepn **tyrosine kinase** VEGF receptor inhibitor; vascular endothelial growth factor receptor inhibitor pyrazolopyrimidine prep; antitumor pyrazolopyrimidine prepn; angiogenesis pyrazolopyrimidine prepn; antiatherosclerotic pyrazolopyrimidine prepn; macular degeneration pyrazolopyrimidine prepn; diabetic retinopathy pyrazolopyrimidine prepn; antiinflammatory pyrazolopyrimidine prepn

IT Antiarteriosclerotics
(antiatherosclerotics; prepn. of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors)

IT Eye, disease
(diabetic retinopathy; prepn. of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors)

IT Eye, disease
(macula, degeneration, age related; prepn. of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors)

IT Angiogenesis
Anti-inflammatory agents
Antitumor agents
(prepn. of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors)

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(prepn. of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors)

IT 293298-42-7P 293298-43-8P 293298-44-9P 293298-45-0P
293298-46-1P 293298-47-2P 293298-48-3P 293298-49-4P
293298-50-7P 293298-51-8P 293298-52-9P 293298-53-0P
293298-54-1P 293298-55-2P 293298-56-3P 293298-57-4P
293298-58-5P 293298-59-6P 293298-60-9P 293298-61-0P
293298-62-1P 293298-63-2P 293298-64-3P 293298-65-4P
293298-66-5P 293298-67-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors)

IT 5472-49-1, 1-(3-Chloropropyl)piperidine hydrochloride 5591-70-8, 3-Amino-4-phenylpyrazole 51076-46-1 66521-53-7 91447-40-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors)

IT 216661-46-0P 293298-68-7P 293298-69-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrazolo[1,5-a]pyrimidines as **tyrosine kinase** inhibitors)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:161133 HCAPLUS
DOCUMENT NUMBER: 132:194377
TITLE: Preparation of benzimidazoles and imidazo[4,5-b]pyridines as novel angiogenesis inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Hungate, Randall W.; Cunningham, April M.; Koester, Timothy J.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

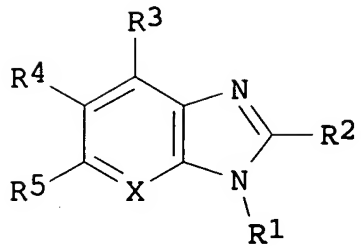
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012089	A1	20000309	WO 1999-US5297	199903 11

W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2341409	AA	20000309	CA 1999-2341409	19990311
AU 9930789	A1	20000321	AU 1999-30789	19990311
AU 760020	B2	20030508		
EP 1109555	A1	20010627	EP 1999-912408	19990311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002523459	T2	20020730	JP 2000-567206	19990311
US 6465484	B1	20021015	US 2001-786004	20010228
PRIORITY APPLN. INFO.:			US 1998-143881 A	19980831
			US 1997-60151P P	19970926
			WO 1999-US5297 W	19990311

OTHER SOURCE(S): MARPAT 132:194377
GI



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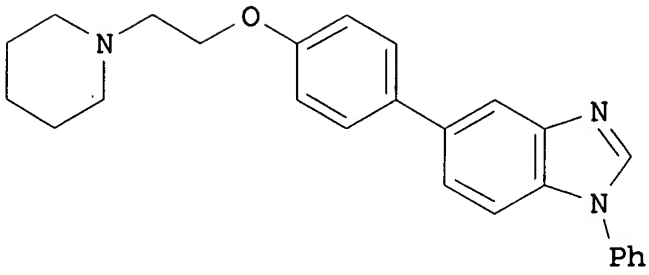


II

AB The title compds. [I; X = N, CH; R1, R3 = H, alkyl, cycloalkyl, etc.; R2 = H, alkyl, aryl, etc.; R4, R5 = H, alkyl, cycloalkyl, etc.] which inhibit **tyrosine kinase** enzymes, and therefore useful in treating **tyrosine kinase** -dependent diseases/conditions such as angiogenesis, cancer, atherosclerosis, diabetic retinopathy or autoimmune diseases, in mammals, were prepd. E.g., a multi-step synthesis of the benzimidazole II was given. Compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 of 150-650 nM.

IC ICM A61K031-44
ICS A61K031-415; A61K031-445; A61K031-495; A61K031-505; A61K031-535; C07D235-10; C07D235-12; C07D235-14; C07D235-16; C07D235-18; C07D235-22; C07D235-24; C07D235-30; C07D239-34; C07D401-10; C07D401-12; C07D401-14; C07D403-10; C07D403-12

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:233907 HCAPLUS
DOCUMENT NUMBER: 130:252359
TITLE: Preparation of benzimidazoles and imidazopyridines as **tyrosine kinase** inhibitors
INVENTOR(S): **Bilodeau, Mark T.**; Hungate, Randall W.; Cunningham, April M.; Koester, Timothy J.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9916755	A1	19990408	WO 1998-US19789	19980922
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2303830	AA	19990408	CA 1998-2303830	19980922
AU 9895003	A1	19990423	AU 1998-95003	19980922
AU 744939	B2	20020307		
EP 1017682	A1	20000712	EP 1998-948427	19980922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
JP 2001518470	T2	20011016	JP 2000-513841	19980922

PRIORITY APPLN. INFO.: US 1997-60151P P

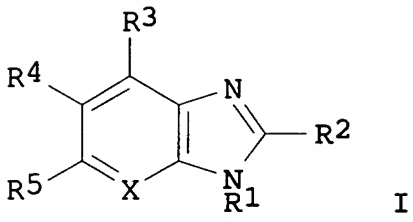
199709
26

GB 1998-10544 A
199805
15

WO 1998-US19789 W
199809
22

OTHER SOURCE(S): MARPAT 130:252359

GI



I

AB The title compds. I [X = N, C; R1 = H, alkyl, cycloalkyl, halo, etc.; R2, R3 = H, alkyl, aryl, OH, etc.; R4 = H, alkyl, alkoxy, alkenyl, etc.; R5 = H, alkyl, halo, etc.], which inhibit **tyrosine kinase** enzymes, were prepd. E.g., 1-phenyl-5-(4-methoxyphenyl)benzimidazole was prepd.

IC ICM C07D235-08
ICS C07D471-04; A61K031-435; A61K031-415
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
ST benzimidazole imidazopyridine prepn **tyrosine kinase** inhibitor
IT 221636-11-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of benzimidazoles and imidazopyridines as **tyrosine kinase** inhibitors)
IT 221636-05-1P 221636-15-3P 221636-16-4P 221636-23-3P
221636-27-7P 221636-28-8P 221636-29-9P 221636-30-2P

221636-31-3P 221636-32-4P 221636-33-5P 221636-34-6P
221636-35-7P 221636-36-8P 221636-37-9P 221636-38-0P
221636-39-1P 221636-40-4P 221636-41-5P 221636-42-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzimidazoles and imidazopyridines as **tyrosine kinase** inhibitors)

IT 80449-02-1, **Tyrosine kinase**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(prepn. of benzimidazoles and imidazopyridines as **tyrosine kinase** inhibitors)

IT 62-53-3, Aniline, reactions 766-11-0 3040-44-6, 1-Piperidineethanol 5720-07-0, 4-Methoxyphenylboronic acid 15862-34-7 33265-79-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of benzimidazoles and imidazopyridines as **tyrosine kinase** inhibitors)

IT 364-73-8P 16588-25-3P 77064-57-4P 221636-02-8P 221636-03-9P 221636-04-0P 221636-08-4P 221636-13-1P 221636-18-6P 221636-20-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of benzimidazoles and imidazopyridines as **tyrosine kinase** inhibitors)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:793092 HCAPLUS
DOCUMENT NUMBER: 130:33028
TITLE: **Tyrosine kinase**-inhibiting pyrazolo[1,5-a]pyrimidine derivatives for angiogenesis inhibitors, preparation, and therapeutic use
INVENTOR(S): **Bilodeau, Mark T.**; Hungate, Randall W.; Kendall, Richard L.; Rutledge, Ruth; Thomas, Kenneth A., Jr.; Rubino, Robert; Fraley, Mark E.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Thomas, Kenneth A., Jr.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9854093	A1	19981203	WO 1998-US10590	19980526
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2291709	AA	19981203	CA 1998-2291709	19980526
AU 9875944	A1	19981230	AU 1998-75944	19980526
EP 984692	A1	20000315	EP 1998-923719	19980526
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002501532	T2	20020115	JP 1999-500790	19980526
US 6235741	B1	20010522	US 1998-86152	19980528
US 6380203	B1	20020430	US 1999-424132	19991118
PRIORITY APPLN. INFO.:			US 1997-48076P P	19970530
			GB 1998-681 A	19980114

WO 1998-US10590 W 199805 26

OTHER SOURCE(S): MARPAT 130:33028

AB Pyrazolo[1,5-a]pyrimidine compds. are provided which inhibit **tyrosine kinases.** Also provided are compns. which contain the **tyrosine kinase**-inhibiting compds. and methods of using the **tyrosine kinase** inhibitors to treat **tyrosine kinase**-dependent diseases/conditions, e.g. angiogenesis, cancer, atherosclerosis, diabetic retinopathy or autoimmune diseases, in mammals. Prepn. of selected pyrazolopyrimidine derivs. is included.

IC ICM C01D239-72
ICS C01D401-00; A01N043-54

CC 1-8 (Pharmacology)
Section cross-reference(s): 28, 63

ST pyrazolopyrimidine deriv prepn **tyrosine kinase** inhibition therapeutic; angiogenesis inhibitor pyrazolopyrimidine deriv prepn; cancer atherosclerosis diabetic retinopathy autoimmune disease pyrazolopyrimidine deriv prepn

IT Lung, neoplasm
Lung, neoplasm
Lung, neoplasm
(adenocarcinoma, inhibitors; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
(brain; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Mammary gland
(carcinoma, inhibitors; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Dermatitis
(contact; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Allergy
(delayed hypersensitivity; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Eye, disease

(diabetic retinopathy; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Blood vessel
(endothelium; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
Antitumor agents
(genitourinary tract tumor inhibitors; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Neuroglia
(glioblastoma, inhibitors; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
(glioblastoma; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Lymphoma
(histiocytic, inhibitors; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Brain, neoplasm
Lung, neoplasm
Pancreas, neoplasm
Pancreas, neoplasm
Stomach, neoplasm
(inhibitors; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
Antitumor agents
(larynx tumor inhibitors; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
Antitumor agents
Antitumor agents
(lung adenocarcinoma; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
(lung small-cell carcinoma; **tyrosine kinase**

-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
(lung; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Lymphatic system
(lymphatic cancer inhibitors; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Eye, disease
(macula, degeneration, age-related; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
(mammary gland carcinoma; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
Antitumor agents
(pancreas; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Drug delivery systems
(prodrugs; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Eye, disease
(retinopathy, vascularization; **tyrosine kinase** -inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Lung, neoplasm
(small-cell carcinoma, inhibitors; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Antitumor agents
(stomach; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT Larynx
Larynx
Urogenital tract
Urogenital tract
(tumor inhibitors; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn.,

and therapeutic use)

IT Angiogenesis inhibitors
Anti-inflammatory agents
Antirheumatic agents
Antitumor agents
Drug delivery systems
Eye, disease
Psoriasis
(**tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT 127464-60-2, Vascular endothelial growth factor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(VEGF-stimulated mitogenesis inhibition; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT 2163-44-2P 2612-32-0P 60813-32-3P 216661-83-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT 3647-69-6, N-(2-Chloroethyl)morpholine hydrochloride 6165-69-1, Thiophene-3-boronic acid 6305-63-1 16461-94-2 65192-28-1 66521-53-7 162286-51-3 216661-87-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; **tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT 216661-57-3P 216661-79-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT 216661-58-4P 216661-80-2P 216661-82-4P 216661-90-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn.,

and therapeutic use)

IT 216661-42-6 216661-44-8 216661-45-9 216661-46-0 216661-48-2
216661-49-3 216661-50-6 216661-51-7 216661-53-9 216661-54-0
216661-55-1 216661-59-5 216661-60-8 216661-61-9 216661-63-1
216661-64-2 216661-65-3 216661-66-4 216661-68-6 216661-70-0
216661-72-2 216661-76-6 216661-84-6 216661-85-7 216661-86-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

IT 80449-02-1, **Tyrosine kinase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**tyrosine kinase**-inhibiting pyrazolopyrimidine derivs. for angiogenesis inhibitors, prepn., and therapeutic use)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l29 ibib abs hitstr hitind 1-2

L29 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:100813 HCAPLUS
DOCUMENT NUMBER: 140:151963
TITLE: Salt forms with tyrosine kinase activity
INVENTOR(S): Ren, Yu; Karki, Shyam B.; Zhao, Matthew M.; Bidodeau, Mark T.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 37 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004023981	A1	20040205	US 2003-607114	20030626

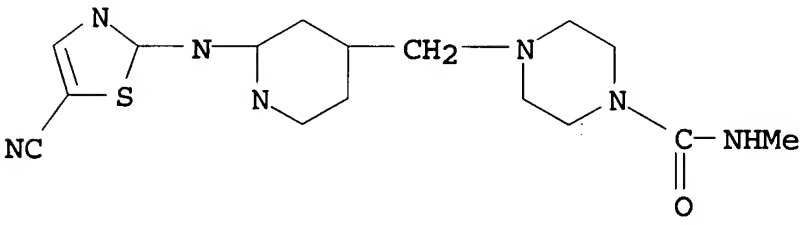
PRIORITY APPLN. INFO.: US 2002-398263P P 200207 24

AB The present invention relates to salt forms of 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide (I) which inhibit, regulate and/or modulate tyrosine kinase signal transduction, and compns. which contain these compds. Methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age-related macular degeneration, diabetic retinopathy, retinal ischemia, macular edema, and inflammatory diseases in mammals. Thus, I was prepd. by the reaction of a piperazine urea with formylpryridine-contg. aminothiazole deriv. followed by redn. The crystal structures of salts of I were studied.

IT **652156-19-9P 652156-20-2P 652156-21-3P**
652156-22-4P 652156-23-5P 652156-24-6P
652156-25-7P 652156-26-8P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(salt forms with tyrosine kinase activity)

RN 652156-19-9 HCAPLUS

CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



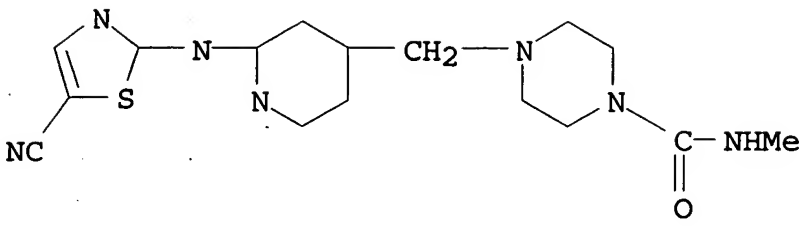
● HCl

ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

RN 652156-20-2 HCAPLUS

CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, monohydrochloride, monohydrate (9CI)

(CA INDEX NAME)



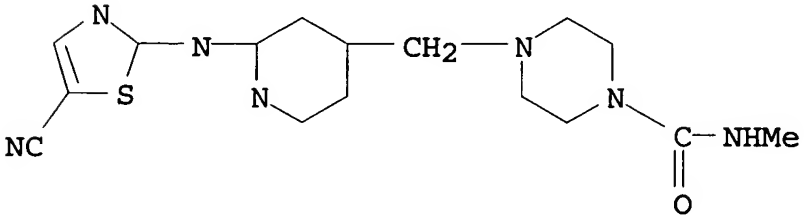
● HCl

● H_2O

ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE
RN 652156-21-3 HCAPLUS
CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, monohydrochloride, compd. with ethanol (1:1) (9CI) (CA INDEX NAME)

CM 1

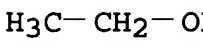
CRN 479611-82-0
CMF C16 H19 N7 O S



ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

CM 2

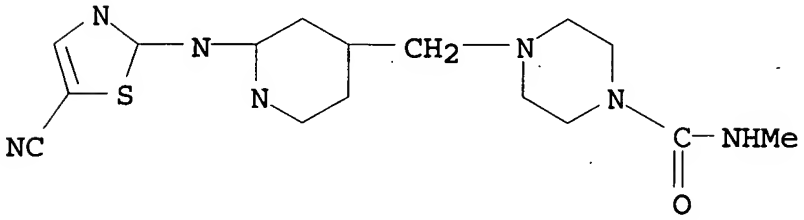
CRN 64-17-5
CMF C2 H6 O



RN 652156-22-4 HCAPLUS
CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 479611-82-0
CMF C16 H19 N7 O S

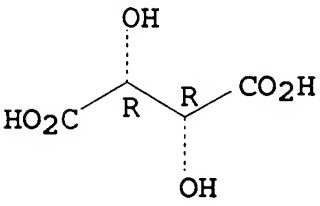


ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

CM 2

CRN 87-69-4
CMF C4 H6 O6

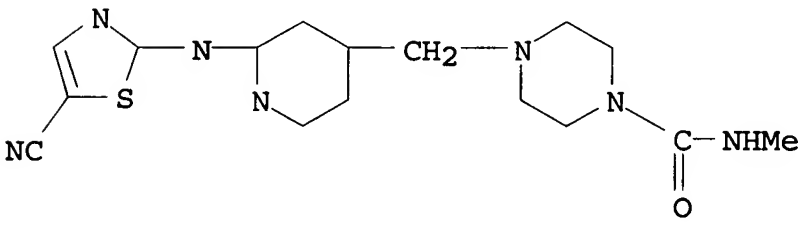
Absolute stereochemistry.



RN 652156-23-5 HCAPLUS
CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1), dihydrate (9CI) (CA INDEX NAME)

CM 1

CRN 479611-82-0
CMF C16 H19 N7 O S

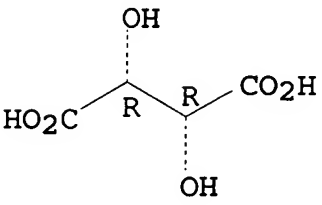


ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

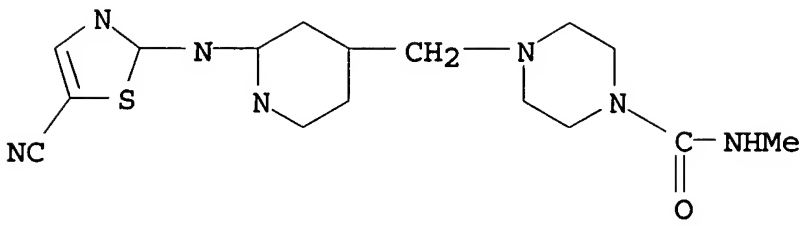


RN 652156-24-6 HCAPLUS
CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 479611-82-0

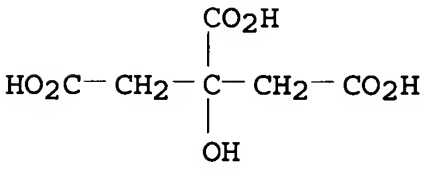
CMF C16 H19 N7 O S



ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

CM 2

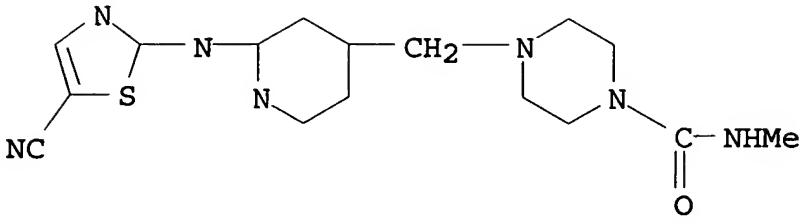
CRN 77-92-9
CMF C6 H8 O7



RN 652156-25-7 HCAPLUS
CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1), monohydrate (9CI) (CA INDEX NAME)

CM 1

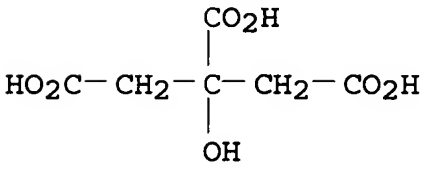
CRN 479611-82-0
CMF C16 H19 N7 O S



ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

CM 2

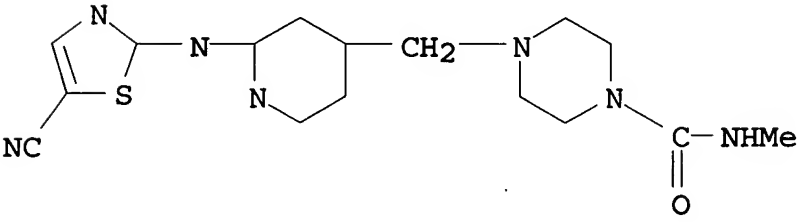
CRN 77-92-9
CMF C6 H8 O7



RN 652156-26-8 HCAPLUS
CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, monobenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

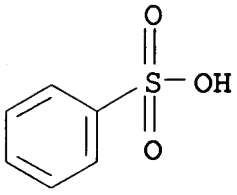
CRN 479611-82-0
CMF C16 H19 N7 O S



ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

CM 2

CRN 98-11-3
CMF C6 H6 O3 S



IC ICM A61K031-496
ICS C07D417-14
INCL 514253100; 544360000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 28
IT 479611-82-0P **652156-19-9P 652156-20-2P**
652156-21-3P 652156-22-4P 652156-23-5P
652156-24-6P 652156-25-7P 652156-26-8P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(salt forms with tyrosine kinase activity)

L29 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:100810 HCAPLUS
DOCUMENT NUMBER: 140:151961
TITLE: Active salt forms with tyrosine kinase activity
INVENTOR(S): Ren, Yu; Karki, Shyam B.; Zhao, Matthew M.; Bilodeau, Mark T.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 2004023978 A1 20040205 US 2003-607031 200306 26

PRIORITY APPLN. INFO.: US 2002-398236P P 200207 24

AB The present invention relates to orally active salt forms of the mesylate salt of 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide (I) which inhibit, regulate and/or modulate tyrosine kinase signal transduction and compns. which contain these compds. Methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, retinal ischemia, macular edema, and inflammatory diseases in mammals are also disclosed. Thus, I was prepd. by the reaction of a piperazine urea with formylpyridine-contg. aminothiazole deriv. followed by redn. The crystal structures of salts of I were studied.

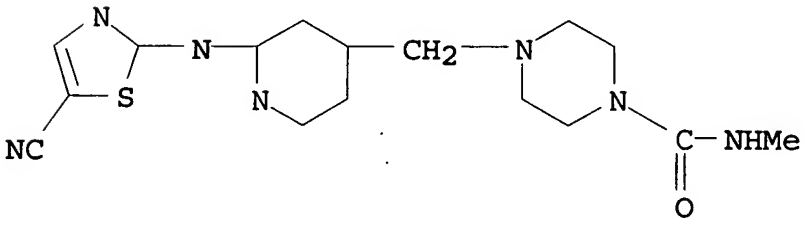
IT **652154-18-2P 652154-19-3P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(active salt forms with tyrosine kinase activity)

RN 652154-18-2 HCAPLUS

CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, monomethanesulfonate (9CI) (CA INDEX NAME)

CM 1

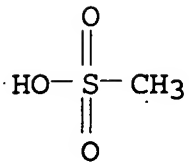
CRN 479611-82-0
CMF C16 H19 N7 O S



ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

CM 2

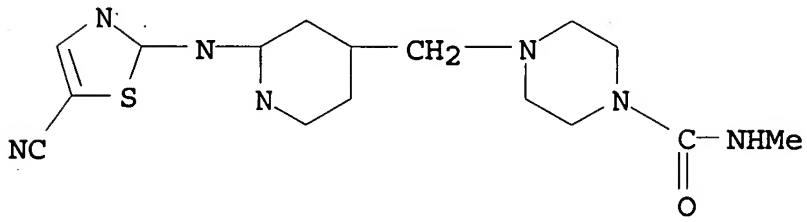
CRN 75-75-2
CMF C H4 O3 S



RN 652154-19-3 HCAPLUS
CN 1-Piperazinecarboxamide, 4-[[2-[(5-cyano-2-thiazolyl)amino]-4-pyridinyl]methyl]-N-methyl-, monomethanesulfonate, monohydrate (9CI) (CA INDEX NAME)

CM 1

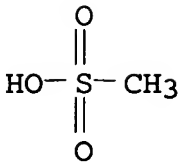
CRN 479611-82-0
CMF C16 H19 N7 O S



ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

CM 2

CRN 75-75-2
CMF C H4 O3 S



IC ICM A61K031-496
ICS C07D417-14
INCL 514253100; 544360000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 28
IT 479611-82-0P **652154-18-2P 652154-19-3P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(active salt forms with tyrosine kinase activity)

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